STATISTICAL INFERENCE FOR MEDICAL COSTS AND INCREMENTAL COST-EFFECTIVENESS RATIOS WITH CENSORED DATA

A Dissertation

by

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ABSTRACT

Cost-effectiveness analysis is widely conducted in the economic evaluation of new treatments, due to skyrocketing health care costs and limited resource available. Censored costs data poses a unique problem for cost estimation due to "induced informative censoring" problem. Thus, many standard approaches for survival analysis are not valid for the analysis of cost data. We first derive the confidence interval for the incremental cost-effectiveness ratio for a special case, when terminating events are different for survival time and costs. Then we study how to intuitively explain some existing estimators for costs, based on the generalized redistribute-to-the-right algorithm. Motivated by that idea, we also propose two improved survival estimators of costs, based on generalized redistribute-to-the-right algorithm and kernel method.

We first consider one special situation in conducting cost-effectiveness analysis, when the terminating events for survival time and costs are different. Traditional methods for statistical inference cannot deal with such data. We propose a new method for deriving the confidence interval for the incremental cost-effectiveness ratio under this situation, based on the counting process theory and the general theory for missing data process. The simulation studies and real data example show that our method performs very well for some practical settings.

In addition, we provide intuitive explanation to a mean cost estimator and a survival estimator for costs, based on generalized redistribute-to-the-right algorithm. Since those estimators are derived based on the inverse probability weighting principle and semiparametric efficiency theory, it is not always easy to understand how these methods work. Therefore, our work engenders a better understanding of those theoretically derived cost estimators.

Motivated by the idea of generalized redistribute-to-the-right algorithm, we propose an estimator for the survival function of costs. The proposed estimator is naturally monotone, more efficient than some existing survival estimators, and has a quite small bias in many realistic settings. We further propose a kernel-based survival estimator for costs. The latter estimator, which is asymptotically unbiased, overcomes the deficiency of the former estimator, while preserving the nice properties. Our proposed estimators outperform existing estimators under various scenarios in simulation and real data example.

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NOMENCLATURE

T	Survival time
C	Censoring time
X	Follow-up time
Δ	Death indicator
$M(t)$	Cost accumulated over time 0 to t
M	Observed cost accumulated until follow-up time X
$S(x)$	Survival function of costs $M(T)$
$S^T(t)$	Survival function of survival time T
$K(t)$	Survival function of censoring time C

TABLE OF CONTENTS

Page

LIST OF FIGURES

LIST OF TABLES

CHAPTER I

INTRODUCTION

Due to skyrocketing of health care costs and limited resource available, economic evaluation of new treatments has received more and more attention. To compare different treatments, cost-effectiveness analysis helps evaluate the economic impact of the new treatment and its effects on health care, in the hope of finding an effective treatment without causing too much burden to the society or individuals.

The analysis of cost data involves some unique challenges that require advanced statistical methodologies, especially when costs are censored. For example, randomized clinical trials often enroll subjects over a broad time period, but the trial ends at a fixed time point. As a result, subjects are observed for differing amounts of time, and those who are still alive at the end of the study are considered censored. Thus, we cannot observe further costs after censored time for those patients. Besides, Censoring poses a unique problem for cost estimation due to the "induced informative censoring" problem, first noted by Lin et al. (1997). Traditional survival analysis methods assume that the censoring time is independent of the survival time (conditional on some covariates). However, the costs at censoring time are no longer independent of the total uncensored costs. For example, a healthier patient will accumulate costs more slowly, and therefore will have less costs at the censoring time, and at the potential event time (Lin, 2003). Thus, many standard approaches for survival analysis, such as the Kaplan-Meier estimator (Kaplan and Meier, 1958), or the Cox regression model (Cox, 1972), are not valid for the analysis of cost data.

Additionally, because of censoring, the costs and survival distribution cannot be estimated over the entire health history, unless more assumptions are imposed.

Hence, many researchers focus on the time-restricted medical costs, i.e., the costs accumulated within a time limit L.

If a program has higher cost but greater benefit than its competitor, a decision must be made on which of the two programs to adopt. In performing cost-effectiveness analysis with censored data, there have been several measures proposed to evaluate the treatments (Chaudhary and Sterns, 1996; Heitjan, 2000; Willan and Lin, 2001; Briggs et al., 2002; O'Brien and Briggs, 2002; Willan and Briggs, 2006). Among them the incremental cost-effectiveness ratio (ICER) is a widely used criterion. The ICER is defined as the costs incurred for saving an additional year of life. However, it is commonly encountered in clinical studies that we need to use different endpoints for costs and effectiveness estimation. For example, a new strategy might prevent the heart failure event. Hence, it may extend the heart-failure free survival time, but not overall survival time. However, we are still interested in the costs estimation up to death. In this situation, we are interested in estimating the ICER based on the heart-failure free survival time but costs accumulated until death. Although the construction for the confidence intervals (CI) of usual ICER with the same terminating points has been studied much, there are no theoretical results for research on this ICER and its CI which allow different terminating events. Thus, we propose a method to handle this problem in Chapter II.

Although many estimators for the mean costs have appeared in the literature, they are often based on theory, and it is not always easy for practitioners to understand why these methods work. To alleviate this situation, Zhao et al. (2011) established a mathematical equivalency between the BT estimator for the mean costs (Bang and Tsiatis, 2000), and a replace-from-the-right (RR) algorithm (Pfeifer and Bang, 2005). Thus, the BT estimator, which is based on the inverse probability weighting technique (Horvitz and Thompson, 1952), has a more intuitive explanation from the RR algorithm. Motivated by this idea, we will extend this work by proposing a modified RR algorithm, the RRimp method, which utilizes the cost history information and is therefore generally more efficient than the RR estimator. We will provide a proof of the mathematical equivalence between the RRimp method and an existing estimator for the mean costs, the ZT estimator (Zhao and Tian, 2001). Due to a lack of a theoretical background for understanding the BT and ZT estimators, some practitioners might be reluctant to use them. With the easy interpretation of the RR and RRimp estimators, and established equivalency between these estimators and the BT, ZT estimators, we believe these estimators will become more popular among practitioners.

Moverover, since cost data are often highly skewed, it is more desirable to estimate the median and other quantiles of the costs. These quantities can be available if we can estimate the survival function of costs. Using the original redistribute-to-the right algorithm, we propose a RR^S (abbreviated as RR^S for survival estimator) survival estimator for costs, and show that it is equivalent to a simple weighted (SW) survival estimator for costs (Zhao and Tsiatis, 1997; Zhao et al., 2012). We extend this method and propose a RRimp^S survival estimator. Numerical studies will be conducted to compare this RRimp^S survival estimator with the RR^S survival estimator (or equivalent SW estimator), and a more efficient ZT^S survival estimator (Zhao and Tsiatis, 1997; Zhao et al., 2012).

Furthermore, we propose a kernel-based estimator for survival function of costs, the RRimp^K estimator, which is naturally monotone, asymptotically unbiased, and includes the RRimp^S as a special case. The RRimp^K estimator overcomes the deficiency of the RRimp^S estimator, while preserving the nice properties. We will conduct numerical studies to examine the finite sample property of the survival estimators for costs and apply them to a data example from a randomized cardiovascular clinical trial.

The remainder of the dissertation is organized as followed. In Chapter II, we will concentrate on cost-effectiveness analysis, and show how to handle the problem of ICER with different terminating events. In Chapter III, we will discuss the mean cost estimators with corresponding intuitive explanation, as well as the survival function estimators for cost. We will also propose the RRimp^S survival estimator of costs. In Chapter IV, we will further propose the kernel-based RRimp^K estimator for survival function of costs, which improves the RRimp^S estimator substantially. Chapter V is the Summary of this dissertation, which summarizes the innovative methods we proposed in this dissertation.

CHAPTER II

ESTIMATING INCREMENTAL COST-EFFECTIVENESS RATIOS AND THEIR CONFIDENCE INTERVALS WITH DIFFERENT TERMINATING EVENTS FOR SURVIVAL TIME AND COSTS*

II.1 Introduction

With health care costs surging in an environment of limited resources, economic evaluations of new treatment strategies are becoming more and more prevalent. If a program has higher cost but greater benefit than its competitor, a decision must be made on which of the two programs to adopt. The incremental cost-effectiveness ratio (ICER) is designed to measure the trade-off between the costs and health benefits of medical interventions. It is defined as the extra costs incurred for saving one additional year of life. The ICER has been the most widely used tool for cost-effectiveness analysis (CEA) (Zwanziger et al., 2006; Wailoo et al., 2008; McIntosh et al., 2009).

Analyzing cost data requires advanced statistical methodologies, especially when cost data are censored. Over a decade has passed since scholars recognized that caution should be exercised when using censored cost data, as described in Lin et al. (1997). The authors point out that traditional methods for handling censored survival data, such as the Kaplan-Meier estimator, Log-rank test, and Cox proportional hazards regression are no longer valid for analyzing censored cost data, due to the "induced informative censoring" problem. Additionally, because of censoring, the

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costs and survival distribution cannot be estimated over the entire health history, unless more assumptions are imposed. Hence, a limited time horizon, such as L (years), is often required, i.e. we measure life-years saved within a limited horizon L, costs within L and hence ICER within L.

Since the ICER is a ratio statistic with quite a skewed distribution, authors often construct a confidence interval (CI) for the ICER in order to estimate its variability. Researchers have proposed various methods for how to find CIs for the ICER. The most widely used in the health service research and health economic literature are bootstrap methods (Efron and Tibshirani, 1986, 1993; Hwang, 1995; Mushlin et al., 1998; Jiang et al., 2000; O'Brien and Briggs, 2002; Jiang and Zhou, 2004); but one can also adapt Fieller's theorem to censored cost data to obtain the CI for the ICER (Fieller, 1954; Chaudhary and Sterns, 1996; Zhao and Tian, 2001; Wang and Zhao, 2008). Although many researchers believe that since the Fieller method is based on the large sample normal assumption, the bootstrap methods provide better coverage, Hwang (1995) and Jiang et al. (2000) showed that both methods are first-order accurate. Therefore, the Fieller method, if used correctly, can be a reliable and efficient way to compute these CIs.

To obtain the CI for the ICER using Fieller's theorem, we need to estimate not only the mean costs and effectiveness (e.g., life expectancies) and their respective variances, but also their covariance. There are proposed methods for estimating the mean medical costs and related variance, and most of these focus on the time-restricted medical costs (Lin et al., 1997; Bang and Tsiatis, 2000; Zhao and Tian, 2001; O'Hagan and Stevens, 2004; Raikou and McGuire, 2004; Zhao et al., 2007, among others). In the construction of CI, a challenge caused by an earlier stopping time for cost collection for some patients has been addressed by Wang and Zhao (2006). However, another challenge arises when the terminating events for costs and survival are different. For example, in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT), the primary goal was to determine whether the cardiac-resynchronization therapy (CRT) with biventricular pacing would reduce the risk of death or heart failure events in patients with mild cardiac symptoms (Moss et al., 2009). The terminating event for the effectiveness measure is death or heart failure (HF), whichever occurs first. Meanwhile, some patients who experienced heart failure events were still living, and continued to accumulate costs and report these costs. Since the treatment costs accumulated until death is of interest, the terminating event for this cost evaluation is a different one, death. We anticipate that more and more medical advances will occur, which may not prolong the overall survival time, but will prevent adverse events such as heart failures. Therefore, ICERs with different terminating events might be used more frequently in the future.

The remainder of this capter is organized as follows. In Section II.2, we propose a method for estimating the ICER and constructing its CI with censored data and different terminating events. In Section II.3, we perform numerical studies to examine the empirical coverage probability of the CI for this special ICER, and compare its performance with bootstrap methods. Next, we illustrate our method by applying it to the MADIT-CRT study. Finally, we provide discussions and concluding remarks.

II.2 Method

II.2.1 Notation and Assumptions

We first concentrate on patients in one arm of the study. For the ith person, let T_i denote the overall survival time, i.e. time until death. In addition, the subject may experience a heart failure event at time HF_i. Let T_i^F denote the HF-free survival time, i.e. the time to a heart failure event or death, whichever occurs first, $T_i^F =$

$\min(HF_i, T_i)$. Let C_i represent the censoring time. Denote the observed follow-up time as $X_i = \min(T_i, C_i)$, and the death indicator as $\Delta_i = I(T_i \leq C_i)$, where $I(\cdot)$ is the indicator function. Similarly, denote the HF-free follow-up time as $X_i^F = \min(T_i^F, C_i)$, and HF-free survival event indicator as $\Delta_i^F = I(T_i^F \leq C_i)$. Let $M_i(u)$ be the costs accumulated over time u. For simplicity, we denote $M_i = M_i(X_i)$ as the observed total costs.

We assume that the censoring time C_i is independent of the survival time T_i, the heart failure time HF_i, and the cost history process $\{M_i(u),\ u \leq T_i\}$. This assumption is reasonable for a well-conducted clinical trial. Because of censoring, it is impossible to estimate the costs over the entire health history. Therefore, we consider only costs accumulated up to a maximum of L units of time, where L is chosen based on the availability of data. This is equivalent to redefining our survival time as $T_i^L = \min(T_i, L)$, and $T_i^{FL} = \min(T_i^F, L)$. For ease of notation, we suppress the superscript L of T_i^L and T_i^{FL} throughout this chapter.

For each of the two treatment groups, $k = 0, 1$, we observe the following identically distributed, independent data $\{X_i, \Delta_i, X_i^F, \Delta_i^F, M_i(X_i), i = 1, \cdots, n_k\}$; n_k is the number of patients for arm k. Our goal is to estimate the mean cost $\mu^M = E\{M_i(T_i)\}$ and the mean HF-free survival time $\mu^F = E(T_i^F)$ for each of the treatment groups, and to compare the treatment strategies by obtaining the ICER and its CI, based on the estimated differences of μ^M and μ^F from the two groups and their variances and covariances.

II.2.2 Estimating the Mean Costs for Each Group

Here we briefly review the methods for estimating the mean costs accumulated over time L with censored data. Bang and Tsiatis (2000) proposed a consistent estimator based on the inverse probability weighting technique: $\hat{\mu}_{BT}^{M} = \frac{1}{n}\sum_{i=1}^{n} \frac{\Delta_i M_i}{\hat{K}(T_i)}$, where $\hat{K}(T_i)$ is the Kaplan-Meier estimator for the survival function of the censoring time C, $K(u) = Pr(C_i > u)$. This is the simple unpartitioned version, and Bang and Tsiatis (2000) also provided a partitioned estimator BTp.

When cost history is available, the BT estimator is not efficient since it does not use the cost information from censored observations. A more efficient estimator, which is also easy to use, is proposed by Zhao and Tian (2001). The ZT estimator has the following simplified form (Pfeifer and Bang, 2005):

$$\hat{\mu}_{ZT}^{M} = \frac{1}{n}\sum_{i=1}^{n} \frac{\Delta_i M_i}{\hat{K}(T_i)} + \frac{1}{n}\sum_{i=1}^{n} \frac{(1-\Delta_i)\{M_i(C_i) - \overline{M(C_i)}\}}{\hat{K}(C_i)}, \tag{1}$$

where $\overline{M(C_i)} = \sum_{j=1}^{n} I(X_j \geq C_i) M_j(C_i) / \sum_{j=1}^{n} I(X_j \geq C_i)$, which is the average accumulated costs at time C_i of those subjects who are alive at C_i.

Zhao et al. (2007) described the conditions under which the ZT estimator is equivalent to the BTp estimator, as well as the two estimators LinA/B proposed by Lin et al. (1997).

Zhao and Tian (2001) show that the ZT estimator is consistent, and asymptotically normally distributed with variance that can be estimated consistently by

$$\begin{aligned} \hat{Var}(\hat{\mu}_{ZT}^{M}) &= \frac{1}{n^2}\sum_{i=1}^{n} \frac{\Delta_i (M_i - \hat{\mu}_{ZT}^{M})^2}{\hat{K}(T_i)} + \frac{1}{n^2}\int_0^L \frac{dN^C(u)}{\hat{K}(u)^2}\{\hat{G}(M^2,u) - \hat{G}(M,u)^2\} \\ &\quad -\frac{2}{n^2}\int_0^L \frac{dN^C(u)}{\hat{K}(u)^2}[\hat{G}\{MM(u),u\} - \hat{G}(M,u)\hat{G}\{M(u),u\}] \\ &\quad +\frac{1}{n^2}\int_0^L \frac{dN^C(u)}{\hat{K}(u)^2}[\hat{G}^*\{M(u)^2,u\} - \hat{G}^*\{M(u),u\}^2], \end{aligned}$$

where

$$N^C(u) = \sum_{i=1}^{n} N_i^C(u) = \sum_{i=1}^{n} I(X_i \leq u, \Delta_i = 0),$$

$$\hat{G}^*\{Z, u\} = \{\sum_{i=1}^{n} Z_i Y_i(u)\}/Y(u),$$

$$Y(u) = \sum_{i=1}^{n} Y_i(u) = \sum_{i=1}^{n} I(X_i \geq u),$$

and $\hat{G}(Z, u) = \frac{1}{n\hat{S}(u)} \sum_{i=1}^{n} \frac{\Delta_i}{\hat{K}(T_i)} Z_i I(T_i \geq u)$, for any random variable Z, and $\hat{S}(u)$ is the Kaplan-Meier estimator for $S(u)$, the survival distribution of T at time u, using data $(X_i, \Delta_i, i = 1, \cdots, n)$. This variance formula is a simplified form of the original formula given by Zhao and Tian (2001) and Zhao and Wang (2010).

II.2.3 Estimating the Mean HF-free Survival Time for Each Group

The mean survival time up to time L can be obtained by the area under the survival function, i.e., $\hat{\mu}^T = \int_0^L \hat{S}(x)dx$, where $\hat{S}(x)$ is the Kaplan-Meier estimator for $S(u) = Pr(T > u)$. This estimator can be more conveniently obtained (Satten and Datta, 2001; Zhao and Tian, 2001) by

$$\hat{\mu}^T = \frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i T_i}{\hat{K}(T_i)}. \tag{2}$$

Similarly, the mean HF-free survival time can be estimated by

$$\hat{\mu}^F = \frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i^F T_i^F}{\hat{K}^F(T_i^F)}, \tag{3}$$

where $\hat{K}^F(u)$ is the Kaplan-Meier estimator for $K(u) = Pr(C > u)$, the survival distribution of C at time u, using data $(X_i^F, \Delta_i^F, i = 1, \cdots, n)$. Following Zhao and

Tian (2001), its variance can be estimated consistently by

$$\frac{1}{n^2}\sum_{i=1}^{n}\frac{\Delta_i^F(T_i^F-\hat{\mu}^F)^2}{\hat{K}^F(T_i)}+\frac{1}{n^2}\int_0^L\frac{dN^F(u)}{\hat{K}^F(u)^2}[\hat{G}^F\{(T^F)^2,u\}-\hat{G}^F(T^F,u)^2],$$

where

$$N^F(u)=\sum_{i=1}^{n}N_i^F(u)=\sum_{i=1}^{n}I(X_i^F\leq u,\Delta_i^F=0),$$

$$\hat{G}^F(Z,u)=\frac{1}{n\hat{S}^F(u)}\sum_{i=1}^{n}\frac{\Delta_i^F}{\hat{K}^F(T_i^F)}Z_iI(T_i^F\geq u),$$

$\hat{S}^F(u)$ is the Kaplan-Meier estimator for $S^F(u)=\Pr(T_i^F>u)$.

II.2.4 Estimating the ICER and Its Confidence Interval

The ICER is the ratio of the difference of costs and the difference of effects between two treatment groups. Here we use HF-free survival time as the measure of effectiveness. For a two-arm trial, for each group k ($k=0,1$), denote μ_k^M as the mean cost and μ_k^F as the mean HF-free survival time, each limited to a window of time [0, L]. The ICER, which measures the additional costs needed for saving one year of HF-free lifetime, is defined as $\gamma=\frac{\mu_1^M-\mu_0^M}{\mu_1^F-\mu_0^F}$.

The ICER γ can be estimated by plugging in the ZT estimator (1) for the mean cost $\hat{\mu}_k^M$, and the estimator for mean HF-free survival time (3), $\hat{\mu}_k^F$, for each group k, $k=0,1$. We use Fieller's Theorem to obtain CIs for the ICER, similarly to Zhao and Tian (2001). Since asymptotically $x=\hat{\mu}_1^M-\hat{\mu}_0^M$ and $y=\hat{\mu}_1^F-\hat{\mu}_0^F$ are bivariate normally distributed, the $100(1-2\alpha)\%$ confidence limits for the ICER γ are

$$\frac{xy-z_\alpha^2s_{xy}\pm\{(xy-z_\alpha^2s_{xy})^2-(x^2-z_\alpha^2s_{xx})(y^2-z_\alpha^2s_{yy})\}^{1/2}}{y^2-z_\alpha^2s_{yy}}, \quad (4)$$

where s_{xx},s_{yy},s_{xy} are respectively the variances of x and y, and the covariance of x

and y, z_α is the cut-off point with tail area α of the standard normal distribution. If the denominator of (4) is positive, the CI is finite. If the denominator of (4) is negative, meaning that the difference between the effects of two treatments is not statistically significant, the CI for the ICER is exclusive and thus infinite. For a discussion on the interpretation of infinite intervals, see Wang and Zhao (2008).

The variance of x and y, s_{xx} and s_{yy}, can be obtained from results mentioned above, treating two arms as independent samples. The challenge is to find the covariance between x and y, or the covariance between the mean cost estimator and the mean HF-free survival time estimator $\hat{\mu}_k^M$ and $\hat{\mu}_k^F$, due to the different terminating events used here. In Appendix A, we express the mean HF-free survival time estimator $\hat{\mu}_k^F$ and the mean cost estimator $\hat{\mu}_k^M$ in martingale forms, and derive the covariance between them based on the counting process theory and the general theory for missing data process (Fleming and Harrington, 1991; Robins and Rotnitzky, 1992; Robins et al., 1994). We show that the covariance between $\hat{\mu}_k^M$ and $\hat{\mu}_k^F$ can be estimated consistently by

$$\begin{aligned}
& \hat{Cov}(\hat{\mu}^M, \hat{\mu}^F) \\
= & \frac{1}{n^2}\sum_{i=1}^{n}\frac{\Delta_i M_i T_i^F}{\hat{K}(T_i)} - \frac{1}{n^3}\sum_{i=1}^{n}\frac{\Delta_i M_i}{\hat{K}(T_i)}\sum_{i=1}^{n}\frac{\Delta_i^F T_i^F}{\hat{K}^F(T_i^F)} \\
& + \frac{1}{n^2}\int_0^L \frac{dN^F(u)}{\hat{K}^F(u)^2}\{\hat{G}^{F_0}(T^F M, u) - \hat{G}^{F_0}(M,u)\hat{G}^{F_0}(T^F,u)\} \\
& - \frac{1}{n^2}\int_0^L \frac{dN^F(u)}{\hat{K}^F(u)^2}[\hat{G}^{F_0}\{T^F M(u), u\} - \hat{G}^{F_0}\{M(u),u\}\hat{G}^{F_0}(T^F,u)], \qquad (5)
\end{aligned}$$

where $\hat{G}^{F_0}(Z,u) = \frac{1}{n\hat{S}^F(u)}\sum_{i=1}^{n}\frac{\Delta_i}{\hat{K}(T_i)}Z_i I(T_i^F \geq u)$.

II.3 Simulation

We conduct simulation studies to examine the performance of the covariance formula, and the coverage probability of the CI of the ICER that relies on the covariance formula. The overall survival time has an exponential distribution $T \sim exp(10)$, which is the same for both treatment groups. The heart failure time is also exponentially distributed, but is different for each group. $HF \sim exp(6)$ for Group 0, and $HF \sim exp(12)$ for Group 1. Hence Group 1 represents a new treatment which prevents occurrence of heart failures but is not effective in preventing death. The survival time T and heart failure time HF are generated independently and truncated at L=10. The HF-free survival time is defined as $T^F = \min(T, HF)$, as mentioned previously. The censoring time has a uniform distribution, $C \sim Unif(0, 15)$, resulting in 42% censoring for the overall survival time and 24%-30% censoring for the HF-free survival time. The true mean HF-free survival time is 3.49 and 4.58 for Group 0 and Group 1 respectively.

We consider U-shaped sample paths for the costs, similarly to Bang and Tsiatis (2000) and Zhao et al. (2012). The entire time period [0, 10] is partitioned into 10 equal (yearly) intervals. The total costs consist of the initial costs incurred at the beginning of the study, the terminal costs accumulated during the last year before death, the fixed annual costs which do not change for each patient, and the random annual costs which vary from year to year. We consider two scenarios with uniformly distributed costs and log normally distributed costs. For the uniform setting, the initial costs, fixed annual costs, random annual costs, and terminal costs are uniformly distributed in $(1,000, 3,000)$, $(2,000, 4,000)$, $(0, 400)$, $(5,000, 15,000)$ for Group 0, and in $(20,000, 30,000)$, $(2,000, 3,000)$, $(0, 400)$, $(5,000, 15,000)$ for Group 1. For the log normal setting, these costs are log normally distributed with parameters $(8.5, 0.632^2)$, $(8, 0.245^2)$, $(4, 0.245^2)$, and $(8, 0.632^2)$ for Group 0, and $(10.2, 0.632^2)$, $(7.5, 0.245^2)$, $(4, 0.245^2)$, and $(8, 0.632^2)$ for Group 1. The true mean costs for Group 0 and Group 1 are $28,241 and $48,095 under the uniform setting, and $27,932 and $47,133 under the log normal setting. Thus, Group 1 is associated with a longer HF-free survival time, but is also more costly than Group 0, mainly due to large initial costs.

The simulation results based on 2000 runs, and various sample sizes, are summarized in Table 1. We first examine the performance of the covariance estimator. Here SCov represents the sample covariance of mean costs and mean HF-free survival times, and ECov represents the mean of estimated covariance using our formula (5). As expected, the estimated covariances between the cost estimator and the HF-free survival estimator are very close to the sample covariances.

For each run of the simulation study, we calculate also the ICER, the extra costs incurred for saving a year of HF-free survival time, and its confidence interval, within a time limit of $L = 10$ years. We then calculate the coverage probability of the true ICER by the CI over the 2000 simulations, which is also shown in Table 1. We see that for various nominal levels, the empirical coverage probability is very close to the nominal level, especially when the sample size is large.

At the suggestion of one reviewer, we also examined the performance of the bootstrap CIs. For our simulation scenarios, the bootstrap samples lie in the Northeast and Northwest regions of the cost-effectiveness (CE) plane. We consider a naive way of constructing the 100(1-2α)% CI using the bootstrap percentile method, i.e. arranging the bootstrap ICERs in ascending order, and obtain the 100(1-2α)% CI using the upper and lower 100α% cutoff points. We also examine the re-ordered bootstrap method proposed by Wang and Zhao (2008), where the orders of ICER are re-arranged according to their positions from a CE plane before obtaining the

Table 1

Summary of covariance estimation for costs and HF-free survival time, and empirical coverage probability of CI for ICER for different nominal levels (0.95,0.90,0.80) from 2000 simulations

Cost	Sample size	Group	Covariance		Empirical coverage probability for ICER		
			SCov	ECov	0.95	0.90	0.80
Uniform	100	0	187	176	0.938	0.887	0.784
		1	182	193			
	200	0	82	83	0.948	0.897	0.789
		1	107	96			
	400	0	39	41	0.942	0.898	0.794
		1	46	48			
Log normal	100	0	177	196	0.934	0.889	0.788
		1	179	164			
	200	0	95	94	0.946	0.894	0.786
		1	75	81			
	400	0	47	46	0.953	0.897	0.790
		1	39	40			

Note: SCov is the sample covariance of mean cost estimator and mean HF-free survival estimator; ECov is the mean of estimated covariance.

tail cutoff points. The comparison of the three methods is shown in Table 2. The bootstrap percentile has much higher coverage probabilities than the nominal levels, and this poor performance is due to the fact that it always produces finite intervals, which is incorrect when the difference of the effectiveness between two groups is non-significant. The performance of re-ordered bootstrap method is comparable with our method. However, our method runs much faster than the two bootstrap methods (1 minute vs 8 hours).

Table 2

Comparison of empirical coverage probability of CIs of ICERs from 2000 simulations and 100 sample size

Nominal level	Uniform cost			Log normal cost		
	New	Re-ordered	Percentile	New	Re-ordered	Percentile
0.95	0.938	0.933	0.978	0.934	0.941	0.972
0.90	0.887	0.883	0.949	0.889	0.887	0.948
0.80	0.784	0.788	0.889	0.788	0.779	0.892

Note: New is our proposed method; Re-ordered is re-ordered bootstrap percentile method; Percentile is ordinary bootstrap percentile method; The bootstrap replication is 1000.

II.4 A Real Data Example: MADIT-CRT

In MADIT-CRT study, patients were recruited into the study over time, and were randomized into either the implantable cardiac defibrillator (ICD) arm or CRT with an ICD (CRT-ICD) arm in a 2:3 ratio. After the trial was completed, it was shown that CRT-ICD reduces the risk of the occurrence of heart failure or death, especially in patients with left bundle branch block (LBBB) conduction disturbance (Goldenberg et al., 2011; Zareba et al., 2011).

Due to the huge costs associated with the implantation of an ICD, a cost-effectiveness analysis also was conducted based on patients from the US centers, with 503 patients in the ICD arm and 748 in the CRT-ICD arm (Noyes et al., 2013). The goal was to evaluate the cost-effectiveness of the CRT-ICD arm as compared to the ICD only arm, restricted to a 4 year horizon, using both overall survival time, and HF-free survival time as effectiveness measures.

Cost data were collected and available for analysis with start and stop dates for each entry. These were first discounted at a 3% annual rate and then spread out evenly in the interval. These discounted costs were then used to estimate the mean costs within a four-year time horizon using the ZT estimator (1), separately for the CRT-ICD group and ICD group. One hundred and twelve (22%) patients in ICD arm and sixty-five (9%) patients in ICD-CRT arm had heart failures but kept accumulating costs, with average additional costs of $35,040 and $28,360 respectively. Each patient's survival time was also discounted at a 3% annual rate, and then plugged in the formulae (2) or (3) to obtain the average unrestricted year-of-life (YOL), or HF-free YOL, within 4 years. In addition, the ICERs comparing the CRT-ICD group and the ICD group were obtained using both the unrestricted and the HF-free YOL. The results are shown in Table 3.

The average health care expenditures in the CRT-ICD group were higher than the ICD-only group ($62,600 vs $57,050, pvalue=0.0146). The CRT-ICD group had also a larger average HF-Free YOL compared to the ICD group, and the difference (0.26 years) was statistically significant (pvalue=0.0002). These results agreed with the primary study which showed that the CRT-ICD had a significant effect reducing the risk of heart failure events or death. On the other hand, the difference of unrestricted YOL (0.07 years) was not statistically different (pvalue = 0.1052).

The HF-free ICER comparing the CRT-ICD group with the ICD group was $21,100 (95% CI: 3,400, 64,310) per one HF-free YOL saved, using the method

Table 3

Estimated mean accumulated costs and life expectancies, ICERs and CIs, limited to a 4 year time horizon, for MADIT-CRT example

	CRT-ICD	ICD	Difference	95%CI	p-value
Costs($1000)	62.60	57.05	5.55	1.10, 10.00	0.0146
HF-free YOL	3.29	3.02	0.26	0.12, 0.40	0.0002
Unrestricted YOL	3.61	3.54	0.07	-0.01, 0.15	0.1052
				95% CI of ICER	
ICER($1000/yr saved)				New	Bootstrap
Incremental costs for HF-free YOL			21.10	3.40, 64.31	3.38, 62.66
Incremental costs for unrestricted YOL			80.91	—	—

Note: New is our proposed method; Bootstrap denotes the bootstrap percentile method with 1000 bootstrap replications.

we proposed, which is very close to the bootstrap CI, (3,380, 62,660). The panel a of Figure 1 shows the bootstrap samples on the CE plane, as well as the estimated HF-free ICER and 95% CIs. Since the bootstrap samples lie in the Northeast and Southeast regions of the CE plane, we calculated the bootstrap 95% CI by the bootstrap percentile method. The unrestricted ICER comparing the CRT-ICD group with the ICD group was much higher, $80,910 per one overall YOL saved. The 95% CI for the unrestricted ICER using both our method and bootstrap method consists of infinite intervals due to the non-significance of the difference of unrestricted YOL between the two groups, as shown in the panel b of Figure 1.

II.5 Conclusions

In this chapter, we consider an important challenge that arises in an actual cost study performed alongside a clinical trial. In a comparison of the cost-effectiveness of a new treatment strategy, the estimates of the effectiveness of the treatment and the costs of the treatment are based on different terminating events. For example, in the MADIT-CRT study, either a heart failure event or death is used as the ter-

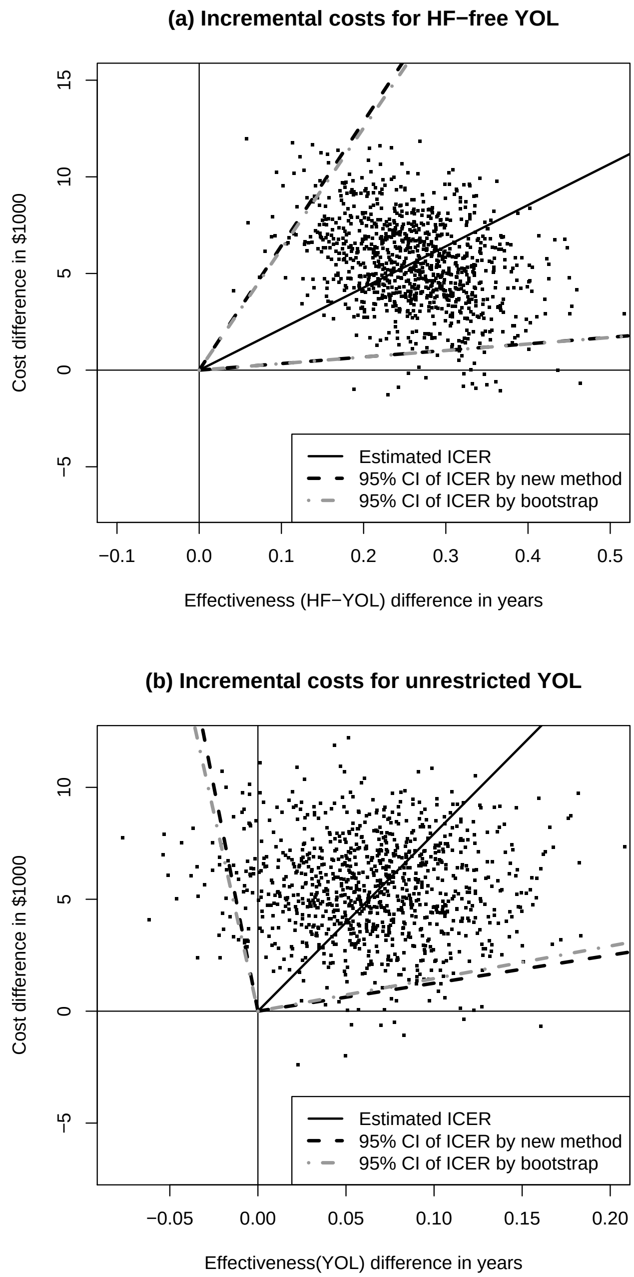

Figure 1. Estimated 95% CIs of HF-free ICER (panel a) and unrestricted ICER (panel b) for the MADIT-CRT study limited to a 4 year time horizon. The dots are 1000 bootstrap samples. The solid line is the estimated ICER; The dashed lines are CI limits obtained by our method; The gray dot-dashed lines are CI limits obtained by bootstrap method. The positive y axis indicates an infinite ICER.

minating event for evaluating the effectiveness of treatment, but death is used for assessing accumulated costs. As in other economic studies conducted in this setting, a censoring problem also complicates the analysis.

We provide a method for estimating consistently the covariance between the costs estimator and the survival estimator under this scenario. This method enables us to construct a correct CI for the ICER. Simulation studies show that our covariance estimator and the CIs perform very well for some practical settings. Our method also accommodates discounting for costs and survival time, and can easily be extended to obtain ICERs and construct their CIs using quality adjusted life years as a measure of effectiveness.

The method we propose here expands the usefulness of ICERs in more flexible settings. Further work may be performed on incorporating covariates information to estimate ICERs, and developing software to facilitate the use of these new methods.

CHAPTER III

GENERALIZED REDISTRIBUTE-TO-THE-RIGHT ALGORITHM: APPLICATION TO THE ANALYSIS OF CENSORED COST DATA*

III.1 Introduction

High and rising health care costs in an environment of limited resources have sharpened the focus on economic evaluation of new treatments. Studies of cost-effectiveness usually aim at evaluating new treatments in the hope of finding an effective treatment that does not cause too much financial burden on society. In clinical trials and observational studies, survival time and health costs frequently are censored for administrative reasons, since not all patients can be observed until events such as death or disease relapse occur. Censoring poses a unique problem for cost estimation due to the "induced informative censoring" problem, first noted by Lin et al. (1997). Traditional survival analysis methods assume that the censoring time is independent of the survival time (conditional on some covariates). However, the costs at censoring time are no longer independent of the total uncensored costs. For example, a healthier patient will accumulate costs more slowly, and therefore will have lower costs at the censoring time and at the potential event time (Lin, 2003). Thus, many standard approaches for survival analysis, such as the Kaplan-Meier estimator (Kaplan and Meier, 1958), or the Cox regression model (Cox, 1972), are not valid for the analysis of cost data.

Many researchers have proposed methods for estimating mean medical costs. Most focus on restricted medical costs, i.e., the costs accumulated within a time

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limit. Among them, Lin et al. (1997) proposed estimators via survival probability weighting using partitioned time intervals; Bang and Tsiatis (2000) proposed consistent estimators using the inverse probability weighting technique; and Zhao and Tian (2001) proposed a more efficient estimator. Later, Zhao et al. (2007) discovered some special conditions under which the estimators without using cost history and those using cost history become identical within each class.

Although many estimators for the mean costs have appeared in the literature, these often are deeply based in theory and therefore less accessible to practitioners. To address this situation, Zhao et al. (2011) established a mathematical equivalency between the BT estimator for the mean costs (Bang and Tsiatis, 2000), and a replace-from-the-right (RR) algorithm (Pfeifer and Bang, 2005). Thus the BT estimator, which is based on the inverse probability weighting technique (Horvitz and Thompson, 1952), has a more intuitive explanation from the point of the RR algorithm. Motivated by this idea, we propose a modified RR algorithm, the RRimp method, which utilizes cost history information and therefore is generally more efficient than the RR estimator. We provide a proof of the mathematical equivalence between the RRimp method and an existing estimator for the mean costs, the ZT estimator (Zhao and Tian, 2001). The ZT estimator was derived from complicated theory. Therefore, the RRimp algorithm provides insight on how the ZT estimator works and eventually can help promote its application in practice.

Cost data are often highly skewed, with most patients incurring relatively small costs, but a few accumulating huge costs. It is often desirable, therefore, to estimate the median and other quantiles of the costs. These quantities are readily available if we can estimate the survival function of costs. Using the original redistribute-to-the right algorithm (Efron, 1967), which was used for explaining the Kaplan-Meier estimator, we propose an RR^S survival estimator for costs, and show that it is equivalent to a simple weighted (SW) survival estimator for costs (Zhao and Tsiatis, 1997; Zhao et al., 2012), which uses the inverse probability weighting technique. We further extend this method to propose an RRimp^S survival estimator. We conduct simulation studies to compare this RRimp^S survival estimator with the RR^S survival estimator (or equivalent SW estimator), and with a more efficient ZT^S survival estimator (Zhao and Tsiatis, 1997; Zhao et al., 2012). We discuss our findings in the Conclusion section.

III.2 Notation and Assumptions

For the ith individual in the study, $i = 1, 2, \ldots, n$, we define T_i as the survival time from the beginning of the study until the occurrence of some event, e.g. death or disease relapse. The censoring time for the ith individual is denoted as C_i. We can observe either the survival time or the censoring time, whichever is shorter, i.e. we observe the follow-up time $X_i = \min(T_i, C_i)$ and the indicator variable $\Delta_i = I(T_i \leq C_i)$. We define $M_i(t)$ as the accumulated cost of patient i from time 0 to t. For some real applications, we observe only the total cost $M_i = M_i(X_i)$. However, in other studies, we may know the entire cost history, $M_i(t), 0 < t < X_i$.

We assume that the censoring variable is independent of the survival time and cost accumulation process, a condition that is often satisfied in well-conducted clinical trials and in some observational studies where censoring occurs mainly for administrative reasons. Due to the presence of censoring, the marginal distribution of cost may be nowhere identifiable without making some parametric assumptions (Huang, 2002). Hence we adopt an approach that focuses on the accumulated cost by a time limit L, where L is chosen such that a reasonable number of subjects are still being observed at that time. A consequence of applying such a restriction is that a survival time longer than L can be considered equivalently as having an event at time L, i.e.

$T_i^L = \min(T_i, L)$ (we still use T_i for notational convenience).

We consider the problem of estimating the mean cost, $\mu = E\{M_i(T_i)\}$, and the survival function of cost, $S(x) = \Pr\{M_i(T_i) > x\}$, for costs accumulated to a time L. For reasons that will become clear below, we also need to define the survival function for the event time as $S^T(t) = \Pr(T_i > t)$, and the survival function for the censoring time as $K(t) = \Pr(C_i > t)$.

III.3 Estimating the Mean Cost

III.3.1 Without Using Cost History: The BT Estimator and Its Equivalent RR Estimator

Bang and Tsiatis (2000) proposed a consistent estimator for the mean costs accumulated over time L with censored data, based on the inverse probability weighting technique:

$$\hat{\mu}_{BT} = \frac{1}{n}\sum_{i=1}^{n}\frac{\Delta_i M_i}{\hat{K}(T_i)}, \qquad (6)$$

where M_i is the total observed cost for the ith individual, and $\hat{K}(T_i)$ is the Kaplan-Meier estimator for the survival function of the censoring time, $K(t) = Pr(C_i > t)$. $K(T_i)$ represents the probability that a subject is uncensored at T_i. The basic idea of the BT estimator is that each complete observation represents potential $1/\hat{K}(T_i)$ observations that might be censored.

Even though the BT estimator is easy to obtain mathematically, for many a full understanding of its mechanism is not very intuitive. The replace-from-the-right (RR) estimator proposed by Pfeifer and Bang (2005), on the other hand, is more so. To explain the main idea of the RR method, first we note that in the absence of censoring, a mean cost estimator is simply the average of costs from all observations. When a subject is censored, we know that this subject lives longer than his/her censoring time, but we do not have information on his/her total cost. In the RR algorithm, we replace this subject's cost by an average of costs from those individuals who survived longer than this subject. Specifically, an RR estimator for the mean costs can be obtained by first arranging all the subjects from the shortest observed time to the longest. If some of these are equal, we put the event time before the (same) censored time. Since we focus on time-restricted cost estimation, we can assume that the individual with the longest observed time is uncensored. We then move from the right (the longest observation time) to the left (the shortest observation time). When we encounter the first censored observation, say, at time C_i, we replace its costs by the average of costs from all the observations to its right,

$$M_i^{RR} = \frac{\sum_{j=1}^n I(X_j > C_i) M_j}{\sum_{j=1}^n I(X_j > C_i)}.$$

We move to the left and repeat this process of replacing all the censored costs with the average of all upstream costs (some of which are real costs and some are replaced costs). The RR mean cost estimator is simply an average of all the costs from both complete observations and censored observations (replaced costs), i.e.

$$\hat{\mu}_{RR} = \frac{1}{n} \sum_{i=1}^{n} \{\Delta_i M_i + (1 - \Delta_i) M_i^{RR}\}. \tag{7}$$

Although the BT estimator (6) and the RR method (7) look quite different – the former is based on a well-known theory, and the latter makes intuitive sense – it is rather amazing that the two estimators in fact are mathematically equivalent. The detailed proof was provided in Zhao et al. (2011).

Note that if we replace the costs M by the survival time T (restricted by time L), we also obtain an equivalency between the RR estimator for the mean (restricted) survival time, and a simple weighted estimator for the mean survival time,

$$\hat{\mu}^T = \frac{1}{n}\sum_{i=1}^{n}\frac{\Delta_i T_i}{\hat{K}(T_i)}.$$

Since this simple weighted estimator has been shown to be equivalent to the area under the Kaplan-Meier survival curve (Satten and Datta, 2001; Zhao and Tian, 2001), we are providing an alternative and simpler way for obtaining the (restricted) area under the Kaplan-Meier survival curve using the RR algorithm.

III.3.2 Using the Cost History: The ZT Estimator and Its Equivalent RRimp Estimator

The BT estimator and its equivalent RR algorithm use only the total cost information from uncensored subjects. Hence, they are not very efficient. An improved estimator proposed by Zhao and Tian (2001) utilizes cost history information from both censored and uncensored observations. Therefore this ZT estimator is often more efficient. It has the following simplified form Pfeifer and Bang (2005):

$$\hat{\mu}_{ZT} = \frac{1}{n}\sum_{i=1}^{n}\frac{\Delta_i M_i}{\hat{K}(T_i)} + \frac{1}{n}\sum_{i=1}^{n}\frac{(1-\Delta_i)\{M_i(C_i) - \overline{M(C_i)}\}}{\hat{K}(C_i)},$$

where $\overline{M(C_i)} = \sum_{j=1}^{n} I(X_j \geq C_i)M_j(C_i)/\sum_{j=1}^{n} I(X_j \geq C_i)$, which is the average cumulative cost at time C_i of those subjects who are alive at C_i.

The ZT estimator consists of two terms. The first is the BT estimator. The second term is constructed using cost history information, which can be viewed as an adjustment term. The ZT estimator gains more efficiency through an adjustment made to the BT estimator using the difference of censored costs and the average accumulated costs at the same time point. Zhao and Tian (2001) established the large sample property for this estimator, and showed that the estimator is consistent and asymptotically normally distributed. Furthermore, Zhao et al. (2007) described the conditions under which this estimator is equivalent to the partitioned Bang and Tsiatis (2000) estimator (BTp), as well as to the two estimators of medical costs LinA/B proposed by Lin et al. (1997).

Since the BT estimator has an intuitive explanation through the RR algorithm, naturally one may wonder whether the ZT estimator has a similar intuitive explanation. Therefore we propose an RRimp algorithm, which makes intuitive sense, and later we show that it is equivalent to the ZT estimator. In contrast to the simple RR method, which depends only on the total costs from complete observations, the RRimp algorithm uses the cost history information from both censored and complete observations. Intuitively, for a censored subject i, we already know his/her accumulated cost before censoring $M_i = M_i(C_i)$. Hence, we need only to estimate his/her cost beyond the censoring time point, $M_i(T_i) - M_i(C_i)$. We propose to impute this cost using the average of all additional costs beyond the censoring point C_i from those subjects who survive longer. The detailed RRimp estimator can be described as follows. First, arrange all the subjects from the shortest to the longest follow-up time. If some of these are the same, we assume events happen shortly before censoring times. Since we focus on time-restricted (say, by L) cost estimation, we assume that the individual with the longest observed time (i.e. L) is uncensored. Starting from the right (the longest observed time) we move to the left. We first find the longest censoring time, denoted as C_i. We replace the cost for this observation by summation of his/her observed costs and the average additional accumulated costs from all subjects who have a longer survival time, i.e.

$$M_i^{RRimp} = M_i + \frac{\sum_{j=1}^{n} I(X_j > C_i)\{M_j - M_j(C_i)\}}{\sum_{j=1}^{n} I(X_j > C_i)}. \tag{8}$$

We then move to the second longest censoring time and perform the same replacement procedure, using the replaced cost for the longest censoring time in calculating the average. We move to the left and repeat this process until we replace all the censored costs. The RRimp estimator is then obtained by an average of costs from all complete observations (real costs) and the censored observations (replaced costs), i.e.

$$\hat{\mu}_{RRimp} = \frac{1}{n} \sum_{i=1}^{n} \{\Delta_i M_i + (1 - \Delta_i) M_i^{RRimp}\}.$$

We illustrate this algorithm using a simple example. Suppose we observe the following data: follow up time $X = \{1, 2, 3, 4, 5\}$, death indicator $\Delta = \{1, 0, 1, 0, 1\}$, and their accumulated costs $M_i(\cdot)$ are shown in Figure 2. Here the 2nd and 4th subjects are censored. In Step 1, we try to obtain the replacement cost for subject 4. Since subject 5 is the only one surviving longer than subject 4, the replacement cost for subject 4 is equal to the summation of the censored cost of subject 4 (= 60) and the additional cost of subject 5 beyond time C_4 (= 40 - 30), which is 70. Similarly, in Step 2 we try to obtain the replacement cost for subject 2 by adding the observed cost of subject 2 (= 50) and the average of additional costs after time C_2 for subject 3 (= 100 - 60, real costs), subject 4 (= 70 - 20, replaced costs) and subject 5 (= 40 - 10, real costs), which is equal to 90. Therefore, the mean cost estimated from the RRimp method gives an estimate of 62, as shown in Figure 2.

Meanwhile, the ZT estimator of the mean cost obtained from the same data set

$X_i =$	1	2	3	4	5
	x	o	x	o	x
$M_1(\cdot) =$	10				
$M_2(\cdot) =$	20	50			
$M_3(\cdot) =$	30	60	100		
$M_4(\cdot) =$	10	20	40	60	
$M_5(\cdot) =$	5	10	20	30	40
Step 1: (M_4^{RRimp})				$70\{= 60 + (40 - 30)\}$	
Step 2: (M_2^{RRimp})		$90\{= 50 + [(100 - 60) + (70 - 20) + (40 - 10)]/3\}$			

$\hat{\mu}_{RRimp} = (10 + 90 + 100 + 70 + 40)/5 = 62.$

Figure 2. An example for the RRimp algorithm.

is:

$$
\begin{aligned}
\hat{\mu}_{ZT} &= \frac{1}{5}\sum_{i=1}^{5}\frac{\Delta_i M_i}{\hat{K}(T_i)} + \frac{1}{5}\sum_{i=1}^{5}\frac{(1-\Delta_i)\{M_i(C_i) - \overline{M(C_i)}\}}{\hat{K}(C_i)} \\
&= \frac{1}{5}(\frac{10}{1} + \frac{100}{3/4} + \frac{40}{3/8}) + \frac{1}{5}(\frac{50-35}{3/4} + \frac{60-45}{3/8}) \\
&= \frac{1}{5}(10 + 400/3 + 320/3) + \frac{1}{5}(20 + 40) \\
&= 50 + 12 = 62,
\end{aligned}
$$

where the Kaplan-Meier estimates for $K(t) = \Pr(C_i > t)$ are $\hat{K}(X_i)$=(1, 3/4, 3/4, 3/8, 3/8), at $X_i = \{1, 2, 3, 4, 5\}$, and $\overline{M(C_i)} = \{35, 45\}$, at $C_i = \{2, 4\}$, respectively. Hence, we obtain exactly the same estimate for the mean costs through both the ZT estimator and the RRimp method using this data set. In Appendix B we provide mathematical proof of the equivalence between the ZT estimator and the RRimp estimator for any data set.

In summary, when censoring of data is present, we cannot observe full costs for every subject. If we have cost history information, we can replace the censored cost by supplementing what we can observe with the average of the additional accumulated costs from upstream observations. This RRimp method is mathematically equivalent to the ZT estimator, and as demonstrated by simulations and examples in Zhao and Tian (2001), is generally more efficient than the BT estimator and its equivalent RR method.

III.4 Estimating Survival Functions for Costs

In addition to estimating the mean costs, we may want to estimate the survival function of costs in practice. The survival function can provide more information about costs, such as medians and quartiles, which are more robust to outliers. Motivated by the idea of the replace-from-the-right algorithm for estimating mean costs, we investigate how to use similar approaches to develop survival estimators for the costs. We show that a naive way of deriving the survival estimator based on the replace-from-the-right algorithm will result in a biased estimator. Instead, we propose a new RR^S estimator for the survival function of costs, based on the original redistribute-to-the-right idea from Efron (1967) for estimating the survival function of a failure time. Within this section only, when the context is clear, we will use the same abbreviation "RR" to stand for redistribute-to-the-right. We will show that the RR^S estimator is equivalent to a simple weighted (SW) survival estimator of costs, whose form was first described in the context of estimating quality-adjusted lifetime by Zhao and Tsiatis (1997). We also attempt to derive a survival estimator RRimp^S based on a modified RR algorithm that uses cost history information. We will discuss the advantages and disadvantages of such an estimator.

III.4.1 The SW Estimator and Its Equivalent RR^S Estimator

Following the work of Zhao and Tsiatis (1997) and Zhao et al. (2012), a SW estimator for the survival function of costs can be obtained by:

$$\hat{S}_{SW}(x) = \frac{1}{n}\sum_{i=1}^{n} \frac{\Delta_i}{\hat{K}(T_i)} I(M_i > x). \tag{9}$$

The large sample properties of this estimator, such as its consistency and asymptotic normality, were established by Zhao and Tsiatis (1997).

To construct an equivalent survival estimator, one is tempted to use the replacement costs at each censoring points and estimate the survival function for costs using the following formula:

$$\hat{S}_{naive}(x) = \frac{1}{n}\sum_{i=1}^{n}\{\Delta_i I(M_i > x) + (1-\Delta_i) I(M_i^{RR} > x)\}. \tag{10}$$

Unfortunately, if we use the empirical distribution function shown above to estimate the survival function for costs, treating the replaced costs as if they were the real costs, the estimated curve will be biased although the area under the curve, i.e., the estimated mean costs, is unbiased. This will be demonstrated in subsequent simulation studies.

In order to find an equivalent RR^S estimator, we rely on the original redistribute-to-the-right idea proposed by Efron (1967), used to explain the Kaplan-Meier estimator for survival time. For each censored subject, since we do not know the actual costs, we will find the contributions from observations that have longer follow-up time than this subject. Specifically, we first sort all subjects according to their observation times from the shortest (left) to the longest (right). For any tied observations, we assume the death event occurs a little earlier than the censored time. We also assume that the individual with the longest observed time is uncensored, since we focus on time-restricted cost estimation. Consider a censored observation i whose initial weight is set to be 1. We distribute its weight evenly to all the time points to its right. For example, if there are n_i such observations, then each one gets a weight of $1/n_i$. Next we find the nearest censored observation to its right, and redistribute its weight again evenly to all the observations to its right. We repeat this process until we have redistributed the weight of the longest censoring time. Note that after redistribution the weights are non-zero only at those complete observations that are on the right side of the censored observation i. Denote the final weight at the jth complete event time as $W_j^{(i)}$, representing the contribution of a complete subject j to the censored subject i.

Due to censoring we often cannot evaluate the mark $I(M_i > x)$. Instead we use the weighted sum

$$I(M_i > x)^{RR} = \sum_{j=1}^{n} \Delta_j I(T_j > X_i) W_j^{(i)} I(M_j > x) \tag{11}$$

as the replacement mark. As a result, the RR^S estimator for the survival function of costs is

$$\hat{S}_{RR}(x) = \frac{1}{n} \sum_{i=1}^{n} \{\Delta_i I(M_i > x) + (1 - \Delta_i) I(M_i > x)^{RR}\}. \tag{12}$$

We illustrate this idea using a simple example. Assume we have data $[X = \{1, 2, 3, 4, 5\},\ \Delta = \{1, 0, 1, 0, 1\},\ M = \{10, 20, 40, 30, 50\}]$. As shown in Figure 3, we first find the weight $W_j^{(2)}$, i.e. the contribution of complete observations to the censored observation 2. In Step 0, the censored observation 2 gets the weight of 1. In Step 1, we distribute its weight of 1 to all of the 3 observations to its right, so

$X_j =$	1	2	3	4	5
	x	o	x	o	x
Step 0:	0	1	0	0	0
Step 1:	0	0	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$
Step 2:	0	0	$\frac{1}{3}$	0	$\frac{2}{3}(= \frac{1}{3} + \frac{1}{3})$
$W_j^{(2)}$:			$\frac{1}{3}$		$\frac{2}{3}$

Figure 3. An example for weights $W_j^{(i)}$.

that each gets a weight of 1/3. Moving to the next censoring time, observation 4, we distribute its weight of 1/3 to the one observation to its right, making the weight at time 5 to be 2/3. Hence we have $W_3^{(2)} = 1/3$, and $W_5^{(2)} = 2/3$.

It is easy to obtain the contributions of complete observations to the censored observation 4, in this case $W_5^{(4)} = 1$. Hence the RR^S estimator is

$$\begin{aligned}
\hat{S}_{RR}(x) &= \frac{1}{5}\sum_{i=1}^{5}\{\Delta_i I(M_i > x) + (1-\Delta_i)I(M_i > x)^{RR}\} \\
&= \frac{1}{5}\{I(M_1 > x) + I(M_3 > x) + I(M_5 > x) \\
&\quad + I(M_2 > x)^{RR} + I(M_4 > x)^{RR}\} \\
&= \frac{1}{5}\{I(M_1 > x) + I(M_3 > x) + I(M_5 > x) \\
&\quad + \frac{1}{3}I(M_3 > x) + \frac{2}{3}I(M_5 > x) + I(M_5 > x)\} \\
&= \frac{1}{5}\{I(M_1 > x) + \frac{4}{3}I(M_3 > x) + \frac{8}{3}I(M_5 > x)\}.
\end{aligned}$$

The simple weighted estimator for this example is

$$\begin{aligned}\hat{S}_{SW}(x) &= \frac{1}{5}\sum_{i=1}^{5}\{\frac{\Delta_i I(M_i > x)}{\hat{K}(T_i)}\} \\ &= \frac{1}{5}\{\frac{I(M_1 > x)}{1} + \frac{I(M_3 > x)}{3/4} + \frac{I(M_5 > x)}{3/8}\} \\ &= \frac{1}{5}\{I(M_1 > x) + \frac{4}{3}I(M_3 > x) + \frac{8}{3}I(M_5 > x)\}.\end{aligned}$$

It is clear that the RR^S estimator is equivalent to the SW survival estimator for costs in this example.

III.4.1.1 Remarks

1. It is not difficult to show that the weight $W_j^{(i)}$ is related to the estimated conditional probability of an event occurring at X_j given that the subject is alive at X_i (discrete case). Thus, $W_j^{(i)}$ can be easily obtained as follows:

   $$W_j^{(i)} = \frac{1}{n\hat{S}^T(C_i)\hat{K}(T_j)},$$

   where $\hat{S}^T(x)$ is the Kaplan-Meier estimator for $\Pr(T > x)$, and $\hat{K}(x)$ is the Kaplan-Meier estimator for $\Pr(C > x)$.

2. We can show that this RR^S estimator (12) for the survival function of costs is mathematically equivalent to the SW estimator based on the similar proofs for mean cost estimators.

3. The weights $W_j^{(i)}$ are exactly the weights needed for obtaining the replaced costs for a censored observation i, in estimating the mean costs by the replace-

from-the-right algorithm, i.e.

$$M_i^{RR} = \sum_{j=1}^{n} \Delta_j I(X_j > X_i) W_j^{(i)} M_j.$$

Therefore, the replace-from-the-right algorithm for the mean cost estimator is a generalized version of the redistribute-to-the-right algorithm.

4. The replaced costs M_i^{RRimp} from the RRimp estimator, however, are not equivalent to

$$\sum_{j=1}^{n} \Delta_j I(X_j > X_i) W_j^{(i)} \{M_i + M_j - M_j(C_i)\}, \tag{13}$$

since M_i^{RRimp} from (8) utilizes the cost information from censored observations beyond C_i while (13) does not.

III.4.2 RR Improved Survival Estimator for the Survival Function of Costs

As in the case of estimating the mean costs, the SW and its equivalent RR^S estimator for the survival function of costs are not efficient since they utilize only the costs from complete observations. Based on the principles of constructing the RR^S survival estimator and the RRimp estimator for mean costs, we propose an improved RR survival (RRimp^S) estimator, as shown below:

$$\hat{S}_{RRimp}(x) = \frac{1}{n} \sum_{i=1}^{n} \{\Delta_i I(M_i > x) + (1 - \Delta_i) I(M_i > x)^{RRimp}\}, \tag{14}$$

where

$$I(M_i > x)^{RRimp} = \sum_{j=1}^{n} \Delta_j I(T_j > X_i) W_j^{(i)} I(M_j^{(i)} > x), \tag{15}$$

is the new replacement mark, and $M_j^{(i)} = M_i + M_j - M_j(C_i)$ is the replacement cost, combining information from censored observation i and complete observation j.

For a censored subject i, if we observe $M_i(C_i) > x$, then we know for sure that $M_i(T_i) > x$. This information is not utilized in the SW estimator (9), or the equivalent RR^S estimator (11). However, it is captured in the RRimp^S estimator (14) and (15), since $M_j^{(i)} = M_i(C_i) + M_j - M_j(C_i) > x$ always holds under $M_i(C_i) > x$, and the sum of weights $W_j^{(i)}$ is 1, giving rise to $I(M_i > x)^{RRimp} = 1$.

Because $I(M_j^{(i)} > x)$ is monotone in x and the weights are non-negative, this RRimp^S estimator is always monotone, which is a desirable property for a survival estimator. In contrast, an improved survival function estimator of costs, ZT^S, first developed by Zhao and Tsiatis (1997) in the context of quality-adjusted survival time, and later applied to cost estimation (Zhao et al., 2012), cannot be guaranteed to be monotone (Huang and Louis, 1998). From subsequent simulation studies and the real example, we see that the RRimp^S estimator is also more efficient, in many practical situations, than both the SW estimator and the ZT^S estimator.

Unfortunately, unlike the SW and the ZT^S estimators, this RRimp^S estimator is not always consistent. An intuitive reason for this inconsistency is as follows. We replace $I(M_j > x)$ by $I(M_j^{(i)} > x)$ in the RRimp^S estimator. Since $M_j(C_i)$ and $M_j - M_j(C_i)$ are dependent, while $M_i(C_i)$ and $M_j - M_j(C_i)$ are independent, the distribution of replaced cost $M_j^{(i)} = M_i(C_i) + M_j - M_j(C_i)$ is different from the distribution of the true cost $M_j = M_j(C_i) + M_j - M_j(C_i)$. As a result, the RRimp^S estimator performs worse when there is a high correlation among costs accumulated in different periods. Nonetheless, the simulation studies show that the bias is quite small, even for the worst-case scenario with a high correlation.

III.5 Simulation Studies

We conduct simulation studies under several different settings to evaluate the survival function estimators for costs. We generate survival times using an exponential distribution $T \sim exp(10)$, and a uniform distribution $T \sim Unif(0, 15)$. The survival time is truncated at L=10. We generate censoring times using a uniform distribution: $C \sim Unif(0, 22)$, for light censoring (25%-30%), and $Unif(0, 15)$, for heavy censoring (37%-44%). The sample size is set to be 100, and the number of simulations is 1000.

We consider U-shaped sample paths for the cost distribution, similar to the simulation settings of Lin et al. (1997); Bang and Tsiatis (2002); Zhao et al. (2012). We partition the entire time period of 10 years into 10 equal intervals. Each individual's costs consist of initial diagnostic costs incurred at time 0, terminal costs incurred during the last year before the failure time, fixed annual costs, and random annual costs (which vary from year to year). The diagnostic costs, fixed annual costs, random annual costs, and terminal costs are generated using a log normal distribution with parameters $(10, 0.245^2)$, $(6, 0.245^2)$, $(4, 0.245^2)$, $(9, 0.632^2)$, respectively. We estimate the survival function of costs using the SW/RR^S estimator, the ZT^S estimator from Zhao and Tsiatis (1997), and our RRimp^S estimator, under the four different simulation scenarios. We also examine the naive survival estimator of (10) for one of the settings.

Figure 4 shows the true survival function for costs and the average of the survival curves from the 1000 simulations using different estimators, for the setting with heavy censoring and exponential survival time. As expected, the SW/RR^S estimator and the ZT^S estimator are both unbiased since they almost coincide with the true survival curve. However the naive estimator, obtained by using the replacement costs as the true costs, is severely biased. We observe similar biases for the naive method under other scenarios.

Figure 5 and Figure 6 display the mean and sample variances of different survival function estimators for costs based on 1000 replications, under four simulation sce-

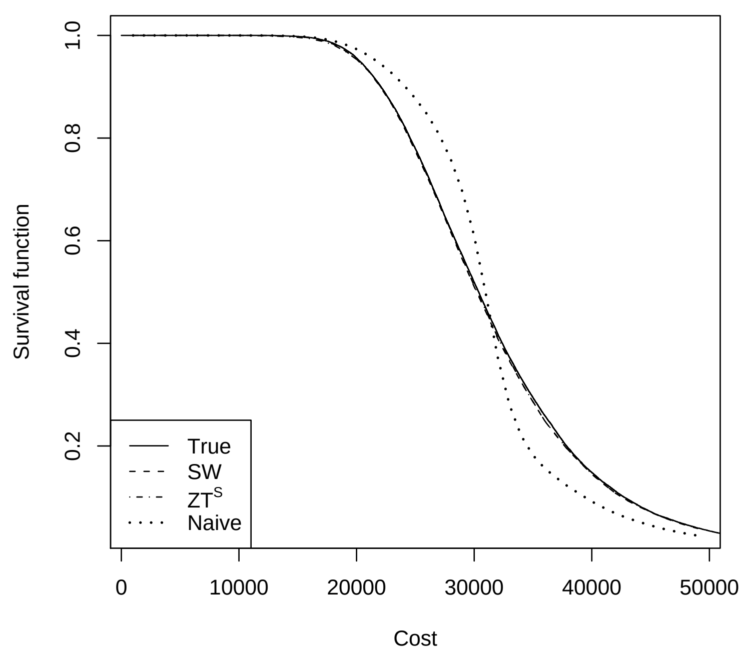

Figure 4. The mean of estimated survival estimators for costs based on 1000 replications with exponential survival time under heavy censoring. The solid curve is the true survival function; the dashed curve is the SW/RR^S estimator; the dot-dashed curve is the ZT^S estimator; the dotted curve is the naive estimator.

narios. The SW/RR^S and ZT^S estimators are consistent as in Figure 4, since these almost coincide with the true survival curve. Although from a theoretical point of view the new proposed RRimp^S estimator is not always consistent, its average survival curves follow the true survival curves very well, for all the settings considered here. This indicates that the bias of the RRimp^S survival estimator is relatively small. In the plots of the sample variances, we find that the ZT^S estimator is more efficient than the SW/RR^S estimator. More importantly, our RRimp^S estimator outperforms both SW/RR^S and ZT^S estimators under all four of these scenarios, with more efficiency gain under heavy censoring. Hence, the RRimp^S survival function makes a significant improvement in efficiency. This improvement is achieved without sacrificing the monotonicity property, unlike in the case of the ZT^S estimator.

Since the RRimp^S survival estimator performs worse when there is a high correlation between costs accumulated in different periods, we design an extreme case in order to examine how biased the RRimp^S estimator could be. We generate the fixed annual costs using a log normal distribution with parameters $(8, 0.245^2)$, while setting the diagnostic costs, random annual costs, and terminal costs to be 0. All other parameters stay the same. Figure 7 displays the mean survival curves and the mean squared errors (MSE = sample variance + bias^2), for the case with exponential survival time and heavy censoring, and for different sample sizes (n = 100, 400). We observe similar trends for other simulation settings. The bias for the RRimp^S estimator is noticeable now, albeit very small. The MSE for the RRimp^S estimator remains mostly the smallest among the three methods available, even when the sample size is as large as 400. In general, as the sample size gets larger, the variance becomes smaller but the bias stays the same. We expect the gain in terms of MSE for the RRimp^S estimator will be most prominent when the sample size is small, or when the censoring rate is high.

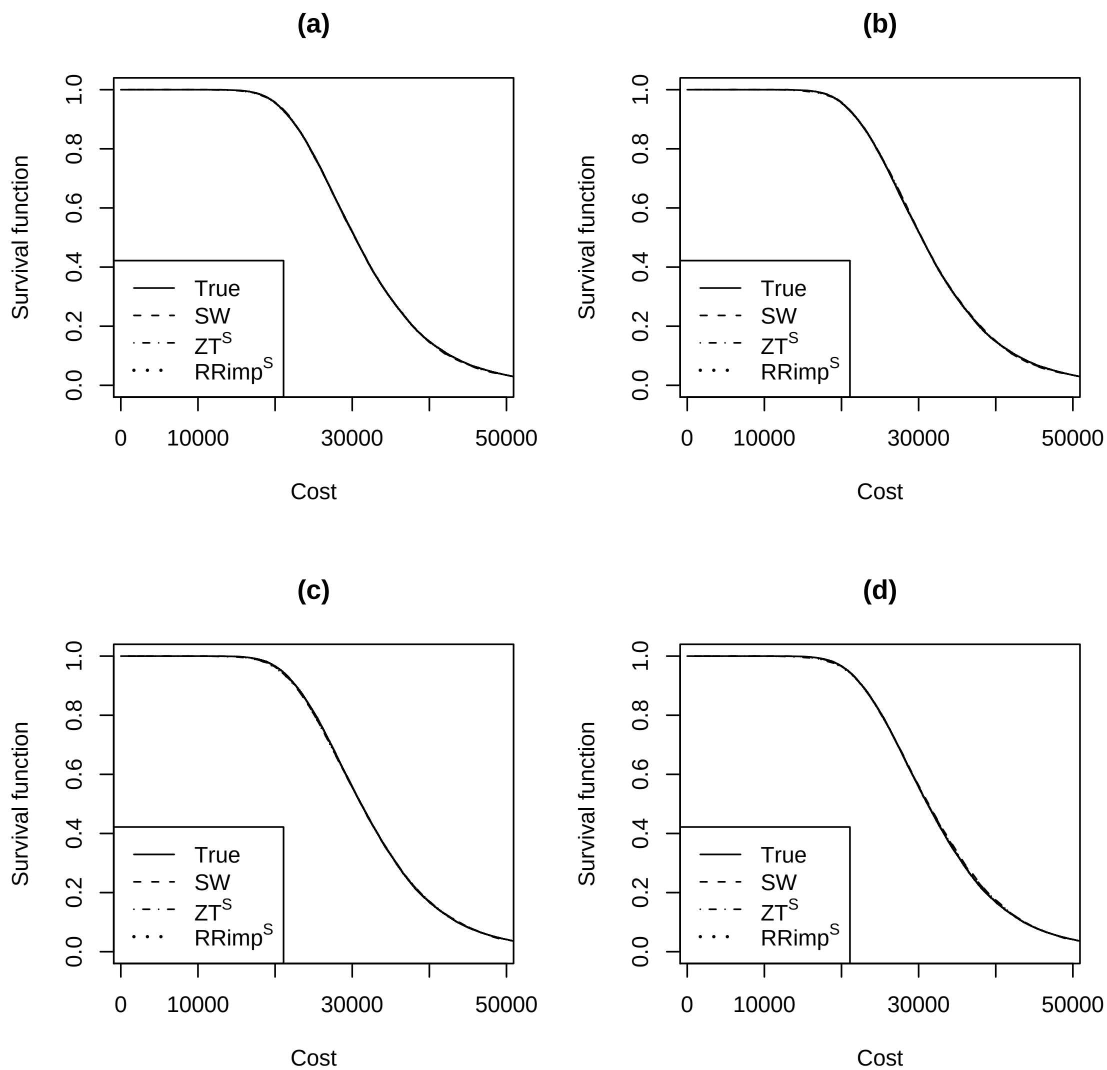

Figure 5. The mean of estimated survival estimators for costs based on 1000 replications. The solid curve is for true survival function; the dashed curve is for SW/RR^S estimator; the dot-dashed curve is for ZT^S estimator; the dotted curve is for RRimp^S estimator. Panel (a) shows the scenario with exponential survival time under light censoring. Panel (b) shows the scenario with exponential survival time under heavy censoring. Panel (c) shows the scenario with uniform survival time under light censoring. Panel (d) shows the scenario with uniform survival time under heavy censoring.

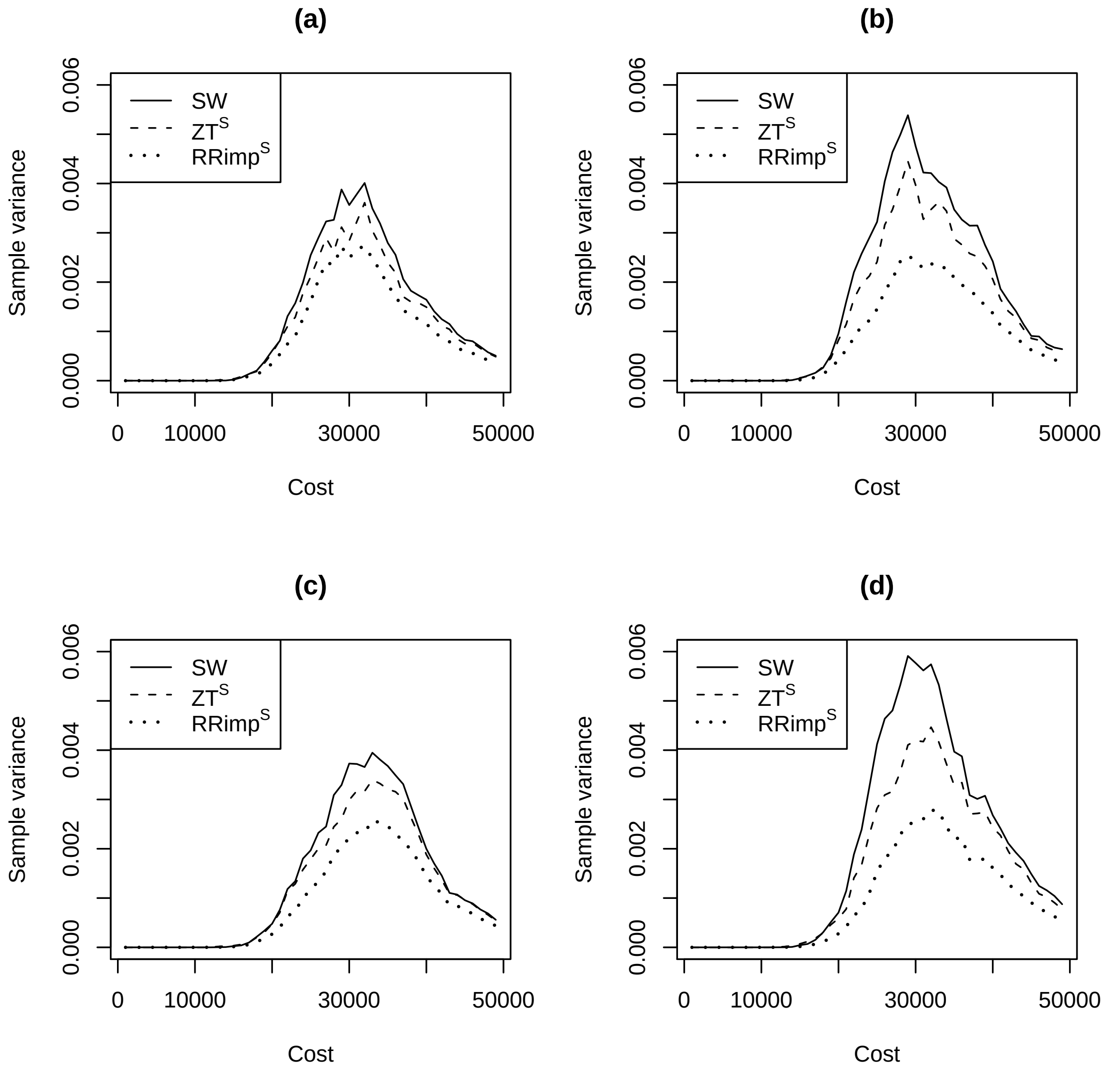

Figure 6. The sample variance of estimated survival estimators for costs based on 1000 replications. The solid curve is for SW/RR^S estimator; the dashed curve is for ZT^S estimator; the dotted curve is for RRimp^S estimator. Panel (a) shows the scenario with exponential survival time under light censoring. Panel (b) shows the scenario with exponential survival time under heavy censoring. Panel (c) shows the scenario with uniform survival time under light censoring. Panel (d) shows the scenario with uniform survival time under heavy censoring.

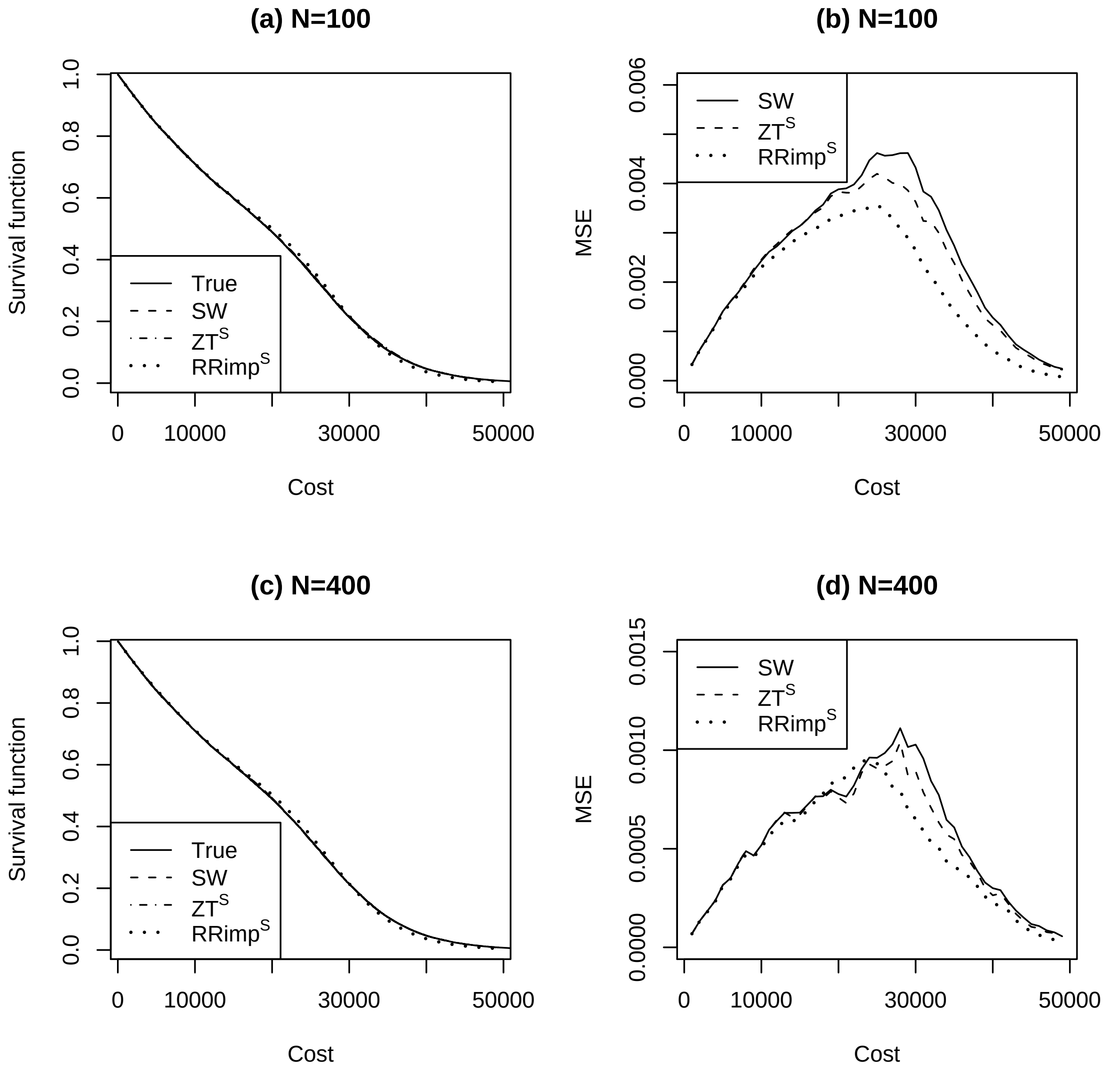

Figure 7. The mean and MSE of estimated survival estimators for costs under the extreme case based on 1000 replications with exponential survival time under heavy censoring. Panel (a) shows the mean of estimated survival estimators for costs with sample size 100. Panel (b) shows the MSE of estimated survival estimators for costs with sample size 100. Panel (c) shows the mean of estimated survival estimators for costs with sample size 400. Panel (d) shows the MSE of estimated survival estimators for costs with sample size 400.

III.6 A Real Data Example: MADIT-II

The Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) was one of a series of studies designed to examine the potential survival benefit of a prophylactically implanted defibrillator in patients with a prior myocardial infarction and other selection criteria (Moss et al., 2002). Patients were recruited into the study over time and were randomized into either the implantable cardiac defibrillator (ICD) arm or the conventional therapy (CONV) arm, with a ratio of 2:1. After the trial was completed, it was shown that the risk of death in the ICD group was lower (hazard ratio=0.69, pvalue =0.016).

Given the huge costs associated with the defibrillator and the implantation process, a cost-effectiveness analysis was conducted based on patients from the US centers, with 664 patients in the ICD arm and 431 in the CONV arm (Zwanziger et al., 2006). The follow-up time varied from 11 days to 55 months, and the average was 22 months. As in their original paper, we examine the costs accumulated over 3.5 years. The estimated survival function for medical costs for the ICD and CONV groups, based on SW/RR^S, ZT^S and RRimp^S estimators, are shown in Figure 8. As mentioned earlier, the ZT^S estimator is not monotone, while both the SW/RR^S and the RRimp^S estimator are monotone. Our RRimp^S survival estimator for cost is also smoother than the SW/RR^S and ZT^S estimators. Figure 9 displays the standard errors of the estimators obtained by the bootstrap method. Similarly to the simulation studies, the standard errors of RRimp^S are mostly the smallest for different costs, and SW/RR^S are the largest. Therefore, our proposed RRimp^S method might be a good alternative for smooth and efficient estimation of the survival function of costs.

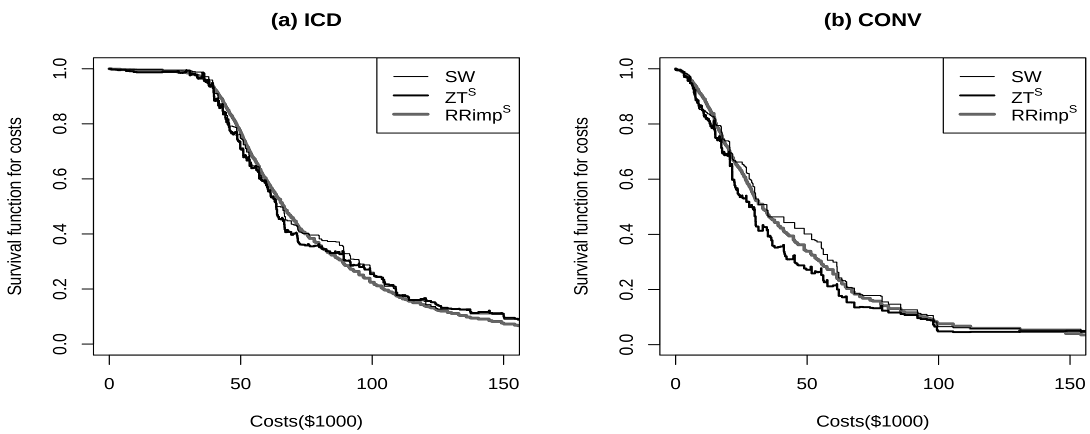

Figure 8. Estimated survival function for medical costs for the MADIT-II study. Panel (a) is for the ICD arm. Panel (b) is for the CONV arm.

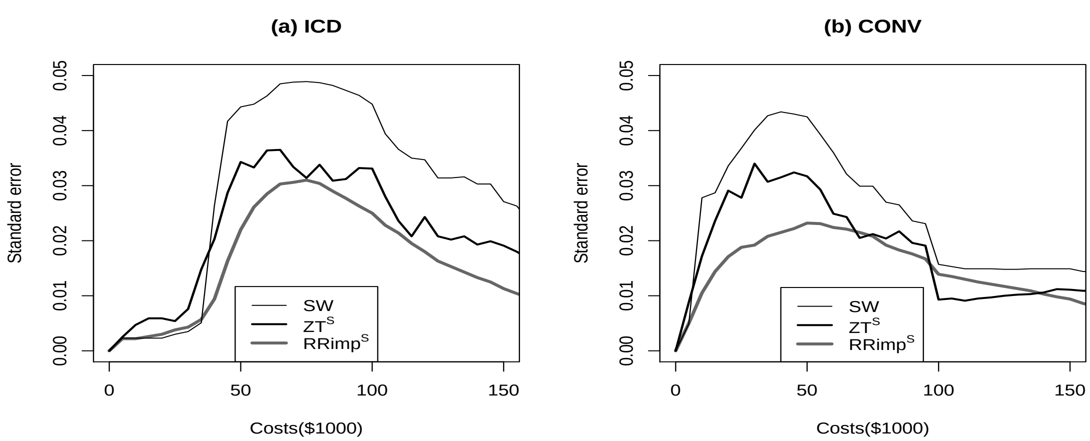

Figure 9. Standard errors (SEs) of the survival estimators for costs obtained by 200 bootstrap replications for the MADIT-II study. Panel (a) shows the SEs for the ICD arm. Panel (b) shows the SEs for the CONV arm.

III.7 Conclusions

In this chapter we extend the research of Zhao et al. (2011), who provided a link between a theoretically justified mean cost estimator based on the inverse probability weighting techniques, that is the BT estimator, and an intuitive replace-from-the-right estimator, the RR estimator. We propose a modified replace-from-the-right algorithm, the RRimp estimator, which utilizes the cost history process and therefore is generally more efficient than the RR estimator. We establish a mathematical equivalency between the RRimp estimator and an improved mean cost estimator, the ZT estimator. In doing so we provide an intuitive explanation for how the ZT estimator works, and thereby engender a better understanding of the theoretically derived mean cost estimators, the BT and ZT estimators. Meanwhile, this paper also gives justification for the simple, intuition-based RR and RRimp estimators. Without the theoretical background for a full understanding of the BT and ZT estimators, some practitioners may hesitate to use these. With a facilitated interpretation of the RR and RRimp estimators, and an established equivalency between these estimators and the BT and ZT estimators, we believe the proposed estimators can become more accessible and useful to practitioners.

Deriving an intuitive estimator for the survival function of costs proves to be a tougher problem. We show that a naive method using the replaced cost as the true cost in an empirical survival function gives rise to a biased estimator. Resorting to the original redistribute-to-the-right idea (Efron, 1967) derived for explaining the Kaplan-Meier estimator, we construct an RR^S survival estimator which can be shown to be equivalent to the SW survival estimator for costs. We also propose an RRimp^S survival estimator which has the desirable property of being monotone, and is usually more efficient than the SW/RR^S survival estimator in many simulation studies and the real example we conducted. Unfortunately, this estimator is not always consistent. Judging from many simulations we conducted, the bias seems to be quite small however. It may be considered as an alternative survival estimator for costs in a real setting when cost history information is available, especially when the sample size is not very large, or the censoring rate is high.

Both the replace-from-the-right and the redistribute-to-the-right algorithms can be viewed as special cases of imputation of missing data. Our work may motivate more research in the area of censored marked variables; quality-adjusted survival time and repeated events are two additional examples. Even though we demonstrated that the proposed RRimp^S estimator was more efficient than the SW estimator in realistic settings, we did not provide theoretical justifications. In our future research we will attempt to develop the standard error estimate of the RRimp^S estimator and to provide theoretical justification for its greater efficiency. We also aim to find a survival estimator for costs that is monotone, consistent, and efficient, if possible.

CHAPTER IV

AN IMPROVED SURVIVAL ESTIMATOR FOR CENSORED MEDICAL COSTS WITH A KERNEL APPROACH

IV.1 Introduction

Rising health care costs in an environment of limited resources have sharpened the focus on economic evaluation of new treatments. Cost-effectiveness analysis usually aims at evaluating competing therapies in the hope of finding an effective treatment that does not cause too much financial burden on individuals or society. In clinical trials and observational studies, survival time and medical costs are frequently censored for administrative reasons, since not all patients can be observed until events such as deaths or disease relapses occur. Censoring poses a unique problem for cost estimation due to the "induced informative censoring" problem, first noted by Lin et al. (1997). Traditional survival analysis methods are only valid under the assumption that the censoring time is independent of the survival time (conditional on some covariates). However, in costs analysis, the costs at censored times are no longer independent of the potential uncensored costs. For example, a healthier patient will accumulate costs more slowly, and therefore will have lower costs at both the censored time and at the potential event time (Lin, 2003). Thus, many standard approaches for survival analysis, such as the Kaplan-Meier estimator, or the Cox regression model, are not valid for the analysis of cost data.

Cost data are often highly skewed, with most patients incurring relatively low costs, but a few people accumulating huge costs. It is often desirable, therefore, to estimate the median and other quantiles of the costs. These quantities are readily available if we can estimate the survival function of costs. The survival function can provide information about costs, such as medians and quartiles, which are more robust to outliers.

Due to the presence of censoring, the marginal distribution of costs may be nowhere identifiable without making some parametric assumptions (Huang, 2002). Thus, we focus on estimating time-restricted medical costs, i.e., the costs accumulated within a time limit. A simple weighted (SW) survival estimator for costs (Zhao and Tsiatis, 1997; Zhao et al., 2012) can be constructed easily using the inverse probability weighting technique. Although it is consistent, and asymptotically normally distributed, it is not efficient due to not using cost history data. Meanwhile, a more efficient ZT^S survival estimator (Zhao and Tsiatis, 1997; Zhao et al., 2012) was first proposed in the setting of estimating quality-adjusted survival time, but it can be applied to the censored costs problem. Unfortunately, this estimator cannot be guaranteed to be monotone. Later, Chen and Zhao (2013) considered a generalized redistribute-to-the-right (RR) algorithm for providing an intuitive explanation for SW estimator, and they proposed a new improved estimator, the RRimp^S estimator. The RRimp^S estimator is usually more efficient than the SW and ZT^S estimators, and always monotone, but unfortunately it is not consistent. In this paper we propose a kernel based survival estimator RRimp^K, which is based on the RRimp^S estimator. We will show that this new estimator overcomes the deficiency, while preserving the desirable properties of RRimp^S (efficiency).

The remainder of this chapter is organized as follows. In Section IV.2, we review previous survival estimators for costs, and then propose the RRimp^K estimator, a kernel-based improved survival estimator for costs. The asymptotic unbiasedness and bandwidth selection for the proposed estimator are also discussed. In Section IV.3, we conduct simulation studies to examine the finite sample properties of the new estimator, and compare it with the SW survival estimator, the ZT^S estimator, and the RRimp^S estimators. In Section IV.4, we apply the survival estimators to a real data example. Finally, we discuss our findings in the Conclusion section.

IV.2 Method

IV.2.1 Notation and Assumptions

For the ith individual in the study, $i = 1, 2, \ldots, n$, we define T_i as the survival time from the beginning of the study until the occurrence of some event, e.g. death or disease relapse. The censoring time for the ith individual is denoted as C_i. We can observe either the survival time or the censoring time, whichever is shorter, i.e. we observe the follow-up time $X_i = \min(T_i, C_i)$ and the indicator variable $\Delta_i = I(T_i \leq C_i)$. We define $M_i(t)$ as the accumulated cost of patient i from time 0 to t. In some applications, we observe only the total cost $M_i = M_i(X_i)$, whereas in other studies, we may know the accumulated costs over the entire history, $M_i(t)$, $(0 < t < X_i)$. We assume the censoring time C is independent of the survival time T and cost process $M(t)$, $(0 < t < T)$. This assumption is usually reasonable in well-conducted clinical trials or observational studies where censoring is mainly caused by administrative reasons.

Due to the presence of censoring, the marginal distribution of costs may be nowhere identifiable without making some parametric assumptions (Huang, 2002). Thus, we adopt an approach that focuses on the accumulated costs by a time limit L, where L is chosen such that a reasonable number of subjects are still being observed at that time. A consequence of applying such a restriction is that a survival time longer than L can be considered equivalently as having an event at time L, i.e. we can redefine the survival time as $T_i^L = \min(T_i, L)$. However, we still use T_i instead of T_i^L for notational convenience.

We consider the problem of estimating the survival function of costs, $S(x) =$

$\Pr\{M_i(T_i) > x\}$, for costs accumulated to a time limit L. For subsequent methodology development, we also need to define the survival function for the event time T as $S^T(t) = \Pr(T_i > t)$, and the survival function for the censoring time as $K(t) = \Pr(C_i > t)$.

IV.2.2 Review of Survival Estimators for Costs

Following the work of Zhao and Tsiatis (1997) and Zhao et al. (2012), a simple weighted (SW) estimator for the survival function of costs can be obtained by using the inverse probability weighting technique:

$$\hat{S}_{SW}(x) = \frac{1}{n}\sum_{i=1}^{n}\frac{\Delta_i}{\hat{K}(T_i)}I(M_i > x),$$

where $\hat{K}(T_i)$ is the Kaplan-Meier estimator for the survival function of the censoring variable C, $K(t) = \Pr(C > t)$, evaluated at T_i. The main idea is that one uncensored observation T_i represents potential $1/K(T_i)$ people that might have been observed.

The SW estimator is good for the case when only the total accumulated costs, instead of the cost history, are available to us. Clearly the SW estimator is not efficient since it does not use the total costs from censored people, nor the cost histories from either censored or complete observations. Meanwhile, a more efficient survival estimator, the ZT estimator (Zhao and Tsiatis, 1997; Zhao et al., 2012), was first proposed for the setting of quality-adjusted survival analysis, but was applied to estimating of the survival function of costs. It used cost history to redefine the endpoint for each person so that the cost information from some censored observations can also make contributions to the cost estimation. For a fixed x, if M_i exceeds x, then this would be known at any time s such that $s \geq s_i(x)$, where $s_i(x) = \inf\,[s : M_i(s) \geq x]$.

Redefine $T_i^*(x) = \min\{T_i, s_i(x)\}$, $\Delta_i^*(x) = I(T_i^*(x) \le C_i)$, the ZT^S estimator is

$$\hat{S}_{ZT}(x) = n^{-1} \sum_{i=1}^{n} \frac{\Delta_i^*(x)}{\hat{K}\{T_i^*(x)\}} I(M_i \ge x).$$

The ZT^S estimator is usually more efficient than the SW estimator, however, it cannot be guaranteed to be monotone.

Generalizing the algorithm of redistribution-to-the-right (RR), which was first discovered for estimating the survival function for failure time with censored data (Efron, 1967), Chen and Zhao (2013) proposed RRimp^S estimator for survival function of costs $S(x)$. It builds on the simple RR estimator which was shown to be equivalent to the SW estimator. The RRimp^S estimator can be written as

$$\hat{S}_{RRimp}(x) = \frac{1}{n} \sum_{i=1}^{n} \{\Delta_i I(M_i > x) + (1 - \Delta_i) I_i^{RRimp}\},$$

where

$$I_i^{RRimp} = \sum_{j=1}^{n} \Delta_j I(T_j > C_i) W_j^{(i)} I(M_j^{(i)} > x),$$

$M_j^{(i)} = M_i(C_i) + M_j - M_j(C_i)$, $W_j^{(i)}$ are adjusting weights,

$$W_j^{(i)} = \frac{1}{n\hat{S}^T(C_i)\hat{K}(T_j)},$$

where $\hat{S}^T(t)$ is the Kaplan-Meier estimator for survival function of survival time $\Pr(T > t)$, and $\hat{K}(t)$ is the Kaplan-Meier estimator for survival function of censoring time $\Pr(C > t)$.

The RRimp^S survival estimator consists of two parts. The first part is the contribution from complete observations. The second part comprises of censored observations indicated by i, whose cost information are borrowed from subjects who have complete cost information and who are still alive at these censored times, with their replacement costs and weights.

The RRimp^S estimator is always monotone, and it has been shown to be generally more efficient than the ZT^S estimator from many simulation studies and a real example (Chen and Zhao, 2013). However, The RRimp^S survival estimator is not consistent, and its performance deteriorates when there is a high correlation between costs accumulated in different time periods.

IV.2.3 Improved Survival Estimator for Costs Using a Kernel Method

The idea of our kernel-based estimator is to improve the precision by incorporating a kernel weight based on the degree of similarity between the complete observation j and the censored observation i, in the second part of the the RRimp^S estimator. We define the similarity as the the distance (difference) of a complete observation's accumulated costs at a censored time, $M_j(C_i)$, from to the censored cost. Specifically, our proposed kernel improved estimator (RRimp^K) is

$$\begin{aligned}\hat{S}_{RRimpK}(x) &= \frac{1}{n}\sum_{i=1}^{n}\Delta_i I(M_i > x) \\ &+\frac{1}{n}\sum_{i=1}^{n}[(1-\Delta_i)\sum_{j=1}^{n}\tilde{w}_h^{(i,j)}\{M_i(C_i)-M_j(C_i)\}I(M_j^{(i)} > x)],\end{aligned}$$

where

$$\tilde{w}_h^{(i,j)}\{M_i(C_i)-M_j(C_i)\} = \frac{\Delta_j I(T_j > C_i) w_h\{M_i(C_i)-M_j(C_i)\}W_j^{(i)}}{\sum_{k=1}^{n}\Delta_k I(T_k > C_i) w_h\{M_i(C_i)-M_k(C_i)\}W_k^{(i)}}$$

are Nadaraya-Watson type weights, and $w_h(x) = \frac{1}{h}w(\frac{x}{h})$ is the kernel function with bandwidth h.

Here the sum of weights in RRimp^K estimator is 1:

$$\sum_{j=1}^{n} \tilde{w}_h^{(i,j)} \{M_i(C_i) - M_j(C_i)\} = 1.$$

As a result, $\hat{S}_{RRimpK}(0) = 1$ can be guaranteed.

It is easy to see that our kernel-based estimator is monotone, since it is a weighted sum of non-increasing indicators. Moreover, the RRimp^S estimator can be viewed as a special case of our RRimp^K estimator with a flat kernel function. In other words, the RRimp^S estimator is an infinite-bandwidth version of our RRimp^K estimator (given certain conditions on the kernel function). As a result, the RRimp^K estimator is always expected to perform not worse than RRimp^S estimator.

IV.2.4 Asymptotic Property of the RRimp^K Estimator

Assume following conditions hold:

(i) For a given censored subject i with censored costs $M_i(C_i)$ and another subject j who is alive at C_i, denote the difference between their accumulated costs at C_i as $u = M_i(C_i) - M_j(C_i)$. The conditional joint density $f(T_j, M_j, u|C_i, M_i(C_i))$ for the jth subject exists and is bounded. Moreover, f is continuous near $u = 0$ for any T and M.

(ii) Assume Markov type property for the cost process, i.e., the conditional distribution of $M(T) - M(t)$ given $M(t)$ is the same for all possible costs accumulation process $M(s), 0 \leq s \leq t$.

(iii) Positive Kernel $\int w(u)\mathrm{d}u < \infty$

(iv) Bandwidth $h_n \to 0$ as $n \to \infty$.

Then at each fixed point x, we have

$$E\{\hat{S}_{RRimpK,n,h_n}(x)\} \to S(x) \text{ as } n \to \infty.$$

We provide a proof for the above result in Appendix C.

IV.2.5 Bandwidth Selections for the RRimp^K Estimator

The bandwidth selection is a challenging problem in kernel-based methods. The following three approaches are widely used.

IV.2.5.1 Rules of thumb method

For instance, a general rule of thumb selects the bandwidth as $h_n = \alpha\sigma n^{-1/3}$, where α is a constant, n is the sample size, $\sigma = SD\{M_j(C_i) - M_i(C_i) : \Delta_i = 0, \Delta_j = 1, T_j > C_i\}$ is the standard deviation of the difference between accumulated costs at the censored place C_i for all (i, j) pairs satisfying the conditions. However, the constant α is unknown and may change according to different model scenarios. One may try various values of α, and identify a range of α that works well for all sample sizes and all model scenarios.

IV.2.5.2 Minimizing the mean integrated squared error

In simulation studies we can calculate the mean integrated squared error (MISE), and select the optimal bandwidth that minimizes the MISE. By using the optimal bandwidth in simulation studies, the researcher can separates the issue of estimator quality from the bandwidth selection problem, and thus demonstrate the advantages of kernel methods more clearly.

IV.2.5.3 Cross-validation method

Li et al. (2013) proposed a cross-validation method for estimator of cumulative distribution function. Following their idea, we can extend their method to survival function for censored cost data, i.e., the selected bandwidth is the one that minimizes

$$\mathrm{CV}_1(h) = \frac{1}{n}\sum_{i=1}^{n} \frac{\Delta_i}{\hat{K}(T_i)} \int \{I(M_i > x) - \hat{S}_{RRimpK,-i}(x)\}^2 dx, \quad (16)$$

where $\hat{S}_{RRimpK,-i}$ is the survival function for costs estimated from data without the ith subject.

In addition to CV_1, we also propose another criteria CV_2 to select the bandwidth by minimizing estimated mean integrated squared error

$$\text{MISE} = \int_0^\infty E\{\hat{S}_{RRimpK}(x) - S(x)\}^2 \mathrm{d}x.$$

Consider the integrated squared error (ISE)

$$\begin{aligned} \text{ISE}(\hat{S}_{RRimpK}) &= \int_0^\infty \{\hat{S}_{RRimpK}(x) - S(x)\}^2 \mathrm{d}x \\ &= I_1 - 2I_2 + I_3, \end{aligned}$$

where $I_1 = \int_0^\infty \{\hat{S}_{RRimpK}(x)\}^2 \mathrm{d}x$, $I_2 = \int_0^\infty \hat{S}_{RRimpK}(x)S(x)\mathrm{d}x$, $I_3 = \int_0^\infty S(x)^2 \mathrm{d}x$. Since I_3 does not depend on the survival estimator, we only focus on I_1 and I_2. A cross-validation idea is to replace I_1 and I_2 by their estimates. Since I_1 is known, we base the estimator of I_2 on the leave-one-out principle.

Let $G(x) = \int_0^x \hat{S}_{RRimpK}(u)\mathrm{d}u$, and denote $F(x) = 1 - S(x)$ as cumulative distribution function of costs.

$$\begin{aligned} I_2 &= \int_0^\infty \hat{S}_{RRimpK}(x)S(x)\mathrm{d}x \\ &= \int_0^\infty S(x)\mathrm{d}G(x) \\ &= G(x)S(x)|_0^\infty - \int_0^\infty G(x)\mathrm{d}S(x) \\ &= 0 + \int_0^\infty G(x)\mathrm{d}F(x). \end{aligned}$$

Therefore, I_2 can be estimated by

$$\hat{I}_2 = \frac{1}{n}\sum_{i=1}^{n} \frac{\Delta_i}{\hat{K}(T_i)} G_{-i}(M_i),$$

where $G_{-i}(x) = \int_0^x \hat{S}_{RRimpK,-i}(u)\mathrm{d}u$, and $\hat{S}_{RRimpK,-i}$ is estimated from data without the ith subject.

Thus, our cross-validation bandwidth is the one that minimizes

$$\begin{aligned} \mathrm{CV}_2(h) &= \hat{I}_1 - 2\hat{I}_2 \\ &= \int_0^{\infty} \{\hat{S}_{RRimpK}(x)\}^2 \mathrm{d}x - \frac{2}{n}\sum_{i=1}^{n} \frac{\Delta_i}{\hat{K}(T_i)} \cdot G_{-i}(M_i). \end{aligned} \tag{17}$$

IV.3 Simulation

As we mentioned previously, the RRimp^S estimator, which has been shown to be usually more efficient than the SW and ZT^S survival estimators, is a special case of our proposed RRimp^K estimator. The RRimp^K estimator is always expected to perform not worse than the RRimp^S estimator. The main problem of the RRimp^S survival estimator is that it is not asymptotically unbiased, and the bias becomes more severe when there is a high correlation between costs accumulated in different time periods. Thus, we design an extreme case in order to examine how biased the RRimp^S estimator could be and how the kernel method could improves.

U-shaped sample paths for the cost distribution have been adopted by Lin et al. (1997); Bang and Tsiatis (2002); Zhao et al. (2012),where the entire time period of 10 years was partitioned into 10 equal intervals. Each individual's costs consist of initial diagnostic costs incurred at time 0, terminal costs incurred during the last year before the failure time, fixed annual costs (which vary from individual to individual), and random annual costs (which vary from year to year). The diagnostic costs, fixed annual costs, random annual costs, and terminal costs are generated using a log normal distribution. Similar scenarios have been employed by Chen and Zhao (2013) to show that the RRimp^S estimator usually has smaller mean squared errors (MSE) than the SW and ZT^S survival estimators, especially with small sample sizes.

To ensure there is a high correlation between costs accumulated in different time periods in the extreme case, we generate the fixed annual costs using a log normal distribution with parameters $(8, 0.245^2)$, while setting the diagnostic costs, random annual costs, and terminal costs to be 0. As a result, the RRimp^S estimator performs badly under this scenario. The survival time has an exponential distribution $T \sim \exp(10)$, truncated at L=10. The censoring times are generated using a uniform distribution $Unif(0, 15)$ for heavy censoring (about 40%). The number of replications is 1000. A Gaussian kernel function is chosen for the RRimp^K estimator $w_h(x) \propto \exp(-\frac{x^2}{2h^2})$, with optimal bandwidth selected by the criteria of smallest MISE.

We examine the performance of the SW (Zhao and Tsiatis, 1997), ZT^S (Zhao and Tsiatis, 1997), RRimp^S (Chen and Zhao, 2013), and our RRimp^K estimators under this extreme case. Figure 10 displays the average survival curves (top two panels), sample variances (middle two panels) and mean squared errors (bottom two panels), for sample sizes of 100 (left three panels) and 400 (right three panels).

It is clear that the RRimp^S estimator is biased in this case, since it does not coincide with the true survival curve. As expected, the kernel method corrects much of the bias and overlaps with the true survival curve. Although the variance of the RRimp^K is slightly bigger than the variance of the RRimp^S at certain areas, for the sample size of 400, it has the smallest MSE among four estimators in our simulation. When sample size is small ($n = 100$), both RRimp^S and our RRimp^K have smaller

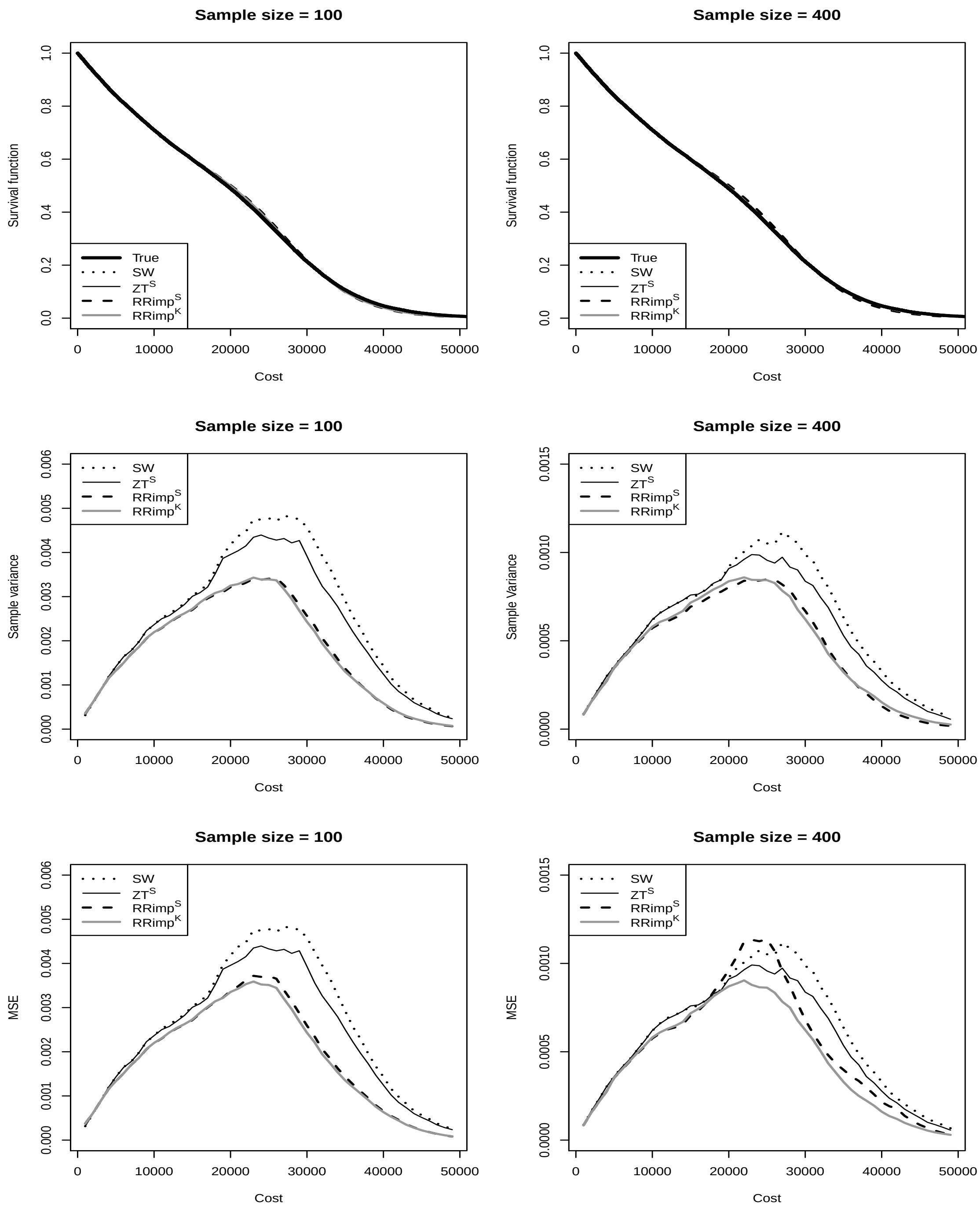

Figure 10. The average survival curves (top two panels), sample variances (middle two panels) and mean squared errors (bottom two panels), for sample sizes of 100 (left three panels) and 400 (right three panels).

MSEs than SW and ZT^S. For a relatively large sample size, e.g. $n = 400$, the MSE is mainly affected by the bias, as a result, the performance of $RRimp^S$ on MSE is worse. Meanwhile, the kernel method corrects much of the bias while still maintains a small sample variance.

Next we examine our data-driven cross-validation (CV) criteria, CV_1 by (16) and CV_2 by (17), and compare them with the MISE method in simulation studies. Table 4 shows the MISEs and average CV values for a range of bandwidths, with the selected bandwidths indicated in bold. On average, the selected bandwidths by CV are the same as those selected using the smallest MISE. Moreover, our simulation shows the kernel estimator is not very sensitive to the bandwidth choice.

Table 4
Comparison between MISEs and average CVs for different bandwidths h in the $RRimp^K$ estimator in simulation

	n=100			n=400		
h	MISE	CV_1	CV_2	MISE	CV_1	CV_2
∞ ($RRimp^S$)	92.21	7170.7	-12321.4	25.68	7073.4	-12382.6
30000	92.00	7170.6	-12321.5	25.56	7073.3	-12383.4
10000	90.96	7170.0	-12321.9	24.90	7072.6	-12383.4
5000	**89.92**	**7169.5**	**-12322.0**	23.97	7071.6	-12384.2
1500	90.47	7171.5	-12318.7	**22.92**	**7070.6**	**-12385.1**
500	93.78	7171.8	-12309.2	22.99	7070.8	-12384.6

IV.4 Example

In the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT), the primary goal was to determine whether the cardiac-resynchronization therapy (CRT) with biventricular pacing would reduce the risk of death or heart failure events in patients with mild cardiac symptoms (Moss et al., 2009). Patients were recruited into the study over time, and were randomized into either the implantable cardiac defibrillator (ICD) arm or CRT with an ICD (CRT-ICD) arm in a 2:3 ratio. After the trial was completed, it was shown that CRT-ICD reduces the risk of the occurrence of heart failure or death, especially in patients with left bundle branch block (LBBB) conduction disturbance (Goldenberg et al., 2011; Zareba et al., 2011).

Due to the huge costs associated with the implantation of an ICD, a cost-effectiveness analysis also was conducted (Noyes et al., 2013), within a four-year time horizon. Cost data were collected and available for analysis with start and stop dates for each entry. These were first discounted at a 3% annual rate and then spread out evenly in the interval. Here we examine the costs accumulated over 4 years from patients with LBBB, with 352 patients in the ICD arm and 507 in the CRT-ICD arm.

We use the cross-validation criteria (16) and (17) to select the bandwidths for the RRimp^K estimators. Table 5 displays the results from these two cross-validation methods for a range of bandwidth for the ICD arm and the CRT-ICD arm, with the selected bandwidths in bold. It indicates that the selected bandwidths are $h = 30,000$ for both arms.

The estimated survival functions for medical costs for the ICD and CRT-ICD groups, based on the SW, ZT^S, RRimp^S and RRimp^K estimators, are shown in Figure 11. Table 6 shows the estimated medians of costs, i.e, $\tau = \inf\{x : \hat{S}(x) \leq 0.5\}$. Figure 12 displays the standard errors of the estimators obtained by the bootstrap method. Similarly to the simulation studies, the standard errors of the RRimp^S estimator (i.e., the RRimp^K estimator with infinite bandwidth) are generally the smallest, and the standard errors of the SW estimator are the largest. The standard errors of the RRimp^K estimators are similar to the RRimp^S estimator. The kernel

Table 5

CV(h) for different bandwidths h in the $RRimp^K$ estimator, for MADIT-CRT example

	ICD		CRT-ICD	
h	CV_1	CV_2	CV_1	CV_2
∞ (RRimp^S)	13502.6	-43307.0	21961.9	-45467.3
100000	13501.0	-43308.5	21959.9	-45469.3
30000	**13499.8**	**-43309.4**	**21947.4**	**-45481.5**
10000	13524.9	-43284.5	21952.5	-45476.1
5000	13535.8	-43274.3	21981.6	-45447.5

method should correct bias while sacrifices some efficiency on variance.

Table 6

Estimated medians of accumulated costs ($1000) over 4 years, for MADIT-CRT example

	SW	ZT^S	RRimp^S	RRimp^K
ICD	48.19	48.57	47.37	47.29
CRT-ICD	52.29	52.96	52.29	51.97

IV.5 Conclusions

In this chapter we extend the research of Chen and Zhao (2013), who provided a survival estimator for costs, the RRimp^S estimator. The RRimp^S survival estimator has the desirable property of being monotone, and is usually more efficient than some existing survival estimators in many simulation studies. Unfortunately, the RRimp^S estimator is not always consistent, although the bias is quite small under most realist scenarios.

In order to overcome this deficiency while preserving the nice properties of the RRimp^S estimator, we proposed an improved survival estimator, the RRimp^K esti-

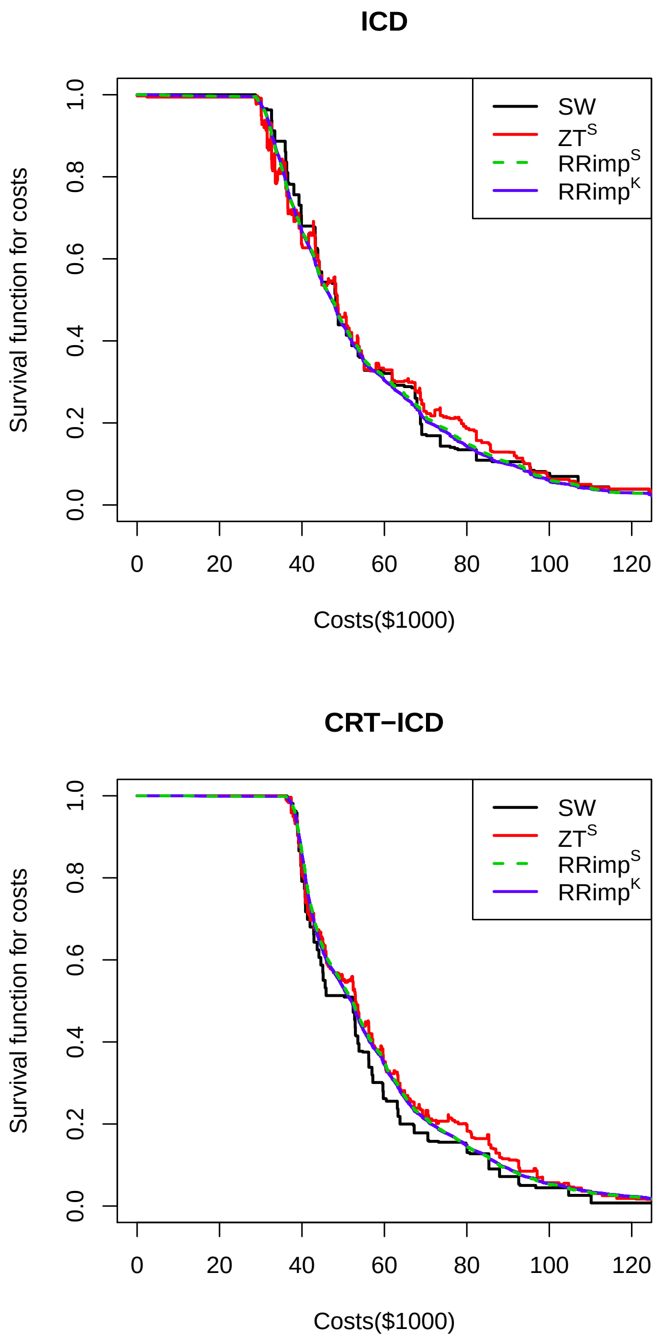

Figure 11. Estimated survival functions for medical costs, for MADIT-CRT study. The top panel is for the ICD arm. The bottom panel is for the CRT-ICD arm.

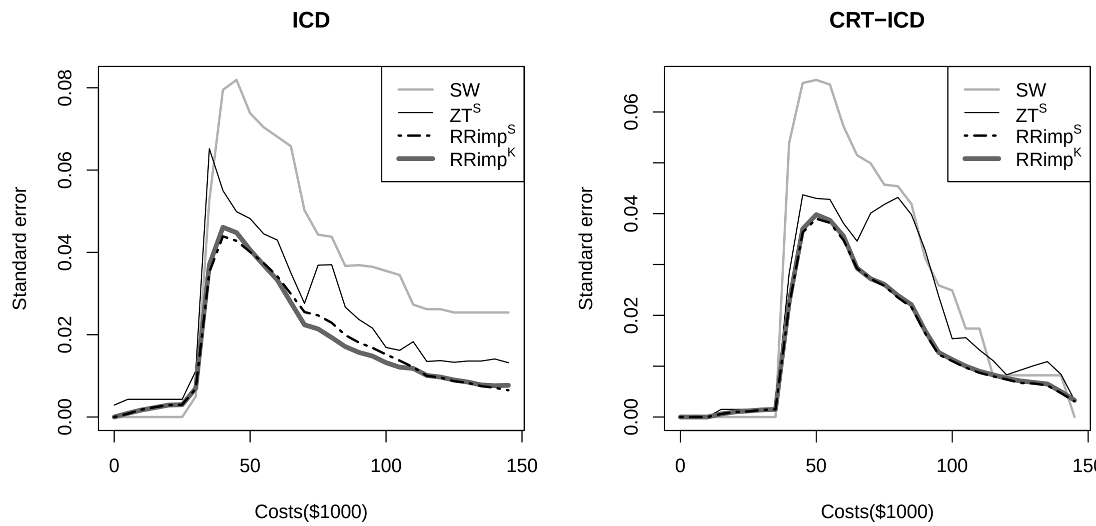

Figure 12. Standard errors (SEs) of the survival estimators for costs obtained by 200 bootstrap replications for the MADIT-CRT study. The left panel is for the ICD arm. The right panel is for the CRT-ICD arm.

mator, through kernel methods. The RRimp^K estimator is monotone and asymptotically unbiased. It includes the RRimp^S estimator as a special case, and it produces the smallest MSE in the simulation studies we conducted, when compared with some existing estimators. When the sample size is small, both the RRimp^S and the RRimp^K estimators perform quite well, producing smaller MSE than the SW and ZT^S estimators; when the sample size is relatively large, the RRimp^K estimator improves the RRimp^S estimator substantially, by correcting the bias through the kernel weighting method.

The new method we propose here expands the tools that are available for medical cost estimation in practice. In the future we will attempt to make our methods more accessible by providing software packages to people who are interested in using these tools. It is our goal to advance the research in the cost-effectiveness field by developing theoretically sound methods that exhibit nice properties in real life applications.

CHAPTER V

SUMMARY

In this dissertation, several innovative methods are proposed for cost estimation and cost-effectiveness analysis with censored data. Censoring brings unique challenges to this field, since we cannot observe complete data for all the subjects in the study. Even though it is reasonable to assume that the censoring and the potential event time are independent (or conditionally independent) for most studies, the "induced informative censoring" problem makes the cost evaluation more difficult, since many standard methods for survival analysis are not appropriate for cost evaluation any more.

In performing cost-effectiveness analysis with censored data, a new challenge arises from having the different terminating events for survival and cost estimation. Therefore, statistical inference for ICER allowing different terminating events is desirable for practitioners to deal with such data. We propose a consistent estimator for this special ICER, as well as a method to construct its CI. The conducted numerical studies show that our method performs very well for some practical settings. Thus, our method provides an effective way to make statistical inference for such data and can easily be extended to obtain ICERs and construct their CIs using quality adjusted life years as a measure of effectiveness.

We then extend the research conducted by Zhao et al. (2011) who provided a link between the BT estimator and an intuitive RR estimator for estimating mean costs with censored data. Our proposed RRimp algorithm utilizes the cost history and therefore is generally more efficient than the RR algorithm. We establish the mathematical equivalency between the RRimp algorithm and an improved mean cost estimator, the ZT estimator. Thus, we are able to provide an intuitive explanation for how the ZT estimator works. We believe our effort enables a better understanding of the theoretically derived mean cost estimators, the BT and ZT estimators, and meanwhile provides justification for the simple, intuition based RR and RRimp estimators.

It is more challenging to derive an intuitive estimator for the survival function of costs. Motivated by the original idea of redistribute-to-the right algorithm (Efron, 1967) for explaining the Kaplan-Meier estimator, we construct a RR^S survival estimator, which can be shown to be equivalent to the SW survival estimator for costs. We also propose a RRimp^S survival estimator which has the desirable property of being monotone, and more efficient than the RR^S survival estimator, but unfortunately, this estimator is not always consistent. Based on kernel method, we further propose an improved survival estimator of costs, the RRimp^K estimator, which is naturally monotone, asymptotic unbiased, and includes the RRimp^S as a special case. The RRimp^K estimator overcomes the deficiency of the RRimp^S estimator, while preserving the nice properties. Therefore, the methods we propose here expand the tools for medical cost estimation in practice. They may be considered as alternative survival estimators for costs in a real setting when cost history information is available.

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APPENDIX A

ESTIMATING THE COVARIANCE BETWEEN THE MEAN COST AND THE MEAN HEART FAILURE FREE SURVIVAL TIME

For ease of notation, we confine our attention to one arm of the study. We define two martingales based on the censoring variable for the survival time and heart failure free survival time, T_i and T_i^F, respectively. For the ith individual, the martingale for the censoring variable for survival time T_i is defined as $M_i^C(u) = N_i^C(u) - \int_0^u \lambda^C(t)Y_i(t)dt$, where $\lambda^C(u)$ is the hazard function for C, $\lambda^C(u) = \lim_{h\to 0} \frac{1}{h}\Pr(C < u+h|C \geq u)$, $Y_i(u) = I(X_i \geq u)$, $N_i^C(u) = I(X_i \leq u, \Delta_i = 0)$. Similarly, the martingale for the censoring variable for heart failure free survival T_i^F is defined as $M_i^{C_F}(u) = N_i^{C_F}(u) - \int_0^u \lambda^C(t)Y_i^F(t)dt$, where $Y_i^F(u) = I(X_i^F \geq u)$, $N_i^{C_F}(u) = I(X_i^F \leq u, \Delta_i^F = 0)$. The filtration $\mathcal{F}(u)$ is defined as the increasing sequence of $\sigma-$algebras generated by

$$\sigma\{I(C_i \leq x), x \leq u; I(T_i \leq s), I(T_i^F \leq s), M_i(s), 0 \leq s < \infty, i = 1, \ldots, n\}.$$

Using results from Zhao and Tian (2001), the improved cost estimator can be expressed approximately by

$$\begin{aligned} & n^{\frac{1}{2}}(\widehat{\mu}^M - \mu^M) \\ = \; & n^{-\frac{1}{2}}\sum_{i=1}^n (M_i - \mu^M) - n^{-\frac{1}{2}}\sum_{i=1}^n \int_0^L \frac{dM_i^C(u)}{K(u)}\{M_i - G(M,u)\} \\ & + n^{-\frac{1}{2}}\sum_{i=1}^n \int_0^L \frac{dM_i^C(u)}{K(u)}[M_i(u) - G\{M(u),u\}] + o_p(1), \end{aligned}$$

where μ^M is the true mean cost, $G(Z,u) = E\{Z_i I(T_i \geq u)\}/S(u)$, for any random variable or functional Z.

The mean heart failure free survival time estimator can be approximated by

$$\begin{aligned} & n^{\frac{1}{2}}(\widehat{\mu}^F - \mu^F) \\ = \ & n^{-\frac{1}{2}}\sum_{i=1}^{n}(T_i^F - \mu^F) - n^{-\frac{1}{2}}\sum_{i=1}^{n}\int_0^L \frac{dM_i^{C_F}(u)}{K(u)}\{T_i^F - G^F(T^F, u)\} + o_p(1), \end{aligned}$$

where μ^F is the true heart failure free survival time, $G^F(Z, u) = E\{Z_i I(T_i^F \geq u)\}/S^F(u)$, for any random variable or functional Z.

To derive the covariance formula between the cost estimator and the survival time estimator, we need to calculate the covariance between the two different martingale processes $< dM_i^C(u), dM_i^{C_F}(u) >$. Define

$$dM_i^{C*}(u) = dN_i^{C*}(u) - \lambda^C(u)I(C_i \geq u)du$$

where $N_i^{C*}(u) = I(C_i \leq u)$. We can show that

$$dM_i^C(u) = I(T_i > u)dM_i^{C*}(u),$$

$$dM_i^{C_F}(u) = I(T_i^F > u)dM_i^{C*}(u),$$

and

$$\text{Var}\{dM_i^{C*}(u)|\mathcal{F}(u)\} = I(C_i > u)\lambda^C(u)du.$$

Hence,

$$\begin{aligned}
& \text{Cov}\{dM_i^C(u), dM_i^{C_F}(u)|\mathcal{F}(u)\} \\
= \;& I(T > u)I(T^F > u)\text{Var}\{dM_i^{C*}(u)|\mathcal{F}(u)\} \\
= \;& Y_i^F(u)\lambda^C(u)du.
\end{aligned}$$

The covariance between the mean cost estimator μ^M and the mean heart failure free survival time estimator μ^F becomes

$$\begin{aligned}
& \text{Cov}\{n^{\frac{1}{2}}(\widehat{\mu}^M - \mu^M), n^{\frac{1}{2}}(\widehat{\mu}^F - \mu^F)\} \\
= \;& \text{Cov}(M_i, T_i^F) + \text{E}\int_0^L \{T_i^F - G^F(T^F, u)\}\{M_i - G(M, u)\}\frac{Y_i^F(u)}{K(u)^2}\lambda^C(u)du \\
& -\text{E}\int_0^L \{T_i^F - G^F(T^F, u)\}\{M_i(u) - G\{M(u), u\}\}\frac{Y_i^F(u)}{K(u)^2}\lambda^C(u)du. \\
= \;& \text{Cov}(M_i, T_i^F) + \text{E}\int_0^L [\{T_i^F - G^F(T^F, u)\}\{M_i - G(M, u)\}I(T_i^F \geq u)]\frac{\lambda^C(u)}{K(u)}du \\
& -\text{E}\int_0^L [\{T_i^F - G^F(T^F, u)\}\{M_i(u) - G\{M(u), u\}\}I(T_i^F \geq u)]\frac{\lambda^C(u)}{K(u)}du. \\
= \;& \text{Cov}(M_i, T_i^F) + \int_0^L [G^F\{T^F M, u\} - G^F\{M, u\}G^F(T^F, u)]\frac{S^F(u)\lambda^C(u)}{K(u)}du \\
& -\int_0^L [G^F\{T^F M(u), u\} - G^F\{M(u), u\}G^F(T^F, u)]\frac{S^F(u)\lambda^C(u)}{K(u)}du
\end{aligned}$$

This can be estimated consistently by

$$
\begin{aligned}
& \frac{1}{n}\sum_{i=1}^{n}\frac{\Delta_i M_i T_i^F}{\widehat{K}(T_i)} - \frac{1}{n^2}\sum_{i=1}^{n}\frac{\Delta_i M_i}{\widehat{K}(T_i)}\sum_{i=1}^{n}\frac{\Delta_i^F T_i^F}{\widehat{K}^F(T_i^F)} \\
+ \quad & \frac{1}{n}\int_0^L \frac{dN^{C_F}(u)}{\widehat{K}^F(u)^2}\{\widehat{G}^{F_0}(T^F M, u) - \widehat{G}^{F_0}(M, u)\widehat{G}^{F_0}(T^F, u)\} \\
- \quad & \frac{1}{n}\int_0^L \frac{dN^{C_F}(u)}{\widehat{K}^F(u)^2}\{\widehat{G}^{F_0}\{T^F M(u), u\} - \widehat{G}^{F_0}\{M(u), u\}\widehat{G}^{F_0}(T^F, u)\},
\end{aligned}
$$

where

$$\widehat{G}^{F_0}(Z, u) = \frac{1}{n\widehat{S}^F(u)}\sum_{i=1}^{n}\frac{\Delta_i}{\widehat{K}(T_i)}Z_i I(T_i^F \geq u),$$

Although some of G can be estimated by

$$\widehat{G}^F(Z, u) = \frac{1}{n\widehat{S}^F(u)}\sum_{i=1}^{n}\frac{\Delta_i^F}{\widehat{K}^F(T_i)}Z_i I(T_i^F \geq u),$$

which seems to adopt more data information when available, using the same form of $\widehat{G}$ achieves more efficiency in numerical studies. Thus, we suggest to use the same estimator for G.

APPENDIX B

PROOF FOR THE EQUIVALENCY OF THE ZT MEAN COST ESTIMATOR AND THE RRIMP METHOD

Suppose we have observed the following survival and cost history data

$$[\{X_i, \Delta_i, M_i, M_i(t_j), \quad j = 1, \cdots, J\}, \quad i = 1, \cdots, n],$$

where i denotes individuals, $t_j (j = 1, \cdots, J)$ denotes the ordered distinctive censoring times. Let Y_j indicate the number of people who have observation times greater than t_j (i.e., $Y_j = \sum_{i=1}^n I(X_i > t_j)$), and n_j represent the number of people who are censored at time t_j. If an event occurs at a censoring time t_j, we assume this event happens shortly before t_j. Therefore, the set $\{X_i = t_j\}$ consist only of censored data.

First, for the subject i who is censored at t_j (note that we allow multiple subjects who are censored at time t_j), define $\delta M_i(t_j)$ as the difference between the observed cost at time t_j for the ith subject and the average accumulated cost at t_j for subjects who are still alive at t_j:

$$\delta M_i(t_j) = M_i(t_j) - \overline{M(t_j)} = M_i(t_j) - \frac{\sum_{i:X_i \geq t_j} M_i(t_j)}{Y_j + n_j}.$$

Define $M^*(t_j)$ as the sum of $\delta M_i(t_j)$ over all subjects who are censored at t_j:

$$\begin{aligned} M^*(t_j) &= \sum_{i:X_i = t_j} \delta M_i(t_j) = \sum_{i:X_i = t_j} M_i(t_j) - n_j \overline{M(t_j)} \\ &= \sum_{i:X_i = t_j} M_i(t_j) - \frac{n_j}{Y_j + n_j} \sum_{i:X_i \geq t_j} M_i(t_j). \end{aligned}$$

Starting from the largest censoring time t_J, there are Y_J subjects who have complete costs and whose survival times are greater than t_J. Hence, the RRimp cost for the kth subject censored at t_J is

$$M_{J,k}^{RRimp} = M_k(t_J) + \frac{1}{Y_J} \sum_{i:X_i > t_J} \{M_i - M_i(t_J)\}.$$

Recall that the replacement cost from RR method for the kth subject censored at time t_J is

$$M_J^{RR} = \frac{1}{Y_J} \sum_{i:X_i > t_J} M_i,$$

thus, the sum of difference between $M_{J,k}^{RRimp}$ (in RRimp method) and M_J^{RR} (in RR method) at t_J is

$$\begin{aligned}
& \sum_{k:X_k = t_J} (M_{J,k}^{RRimp} - M_J^{RR}) \\
= & \sum_{k:X_k = t_J} M_k(t_J) + \frac{n_J}{Y_J} \sum_{i:X_i > t_J} \{M_i - M_i(t_J)\} - \frac{n_J}{Y_J} \sum_{i:X_i > t_J} M_i \\
= & \sum_{i:X_i = t_J} M_i(t_J) - \frac{n_J}{Y_J} \sum_{i:X_i > t_J} M_i(t_J) \\
= & (1 + \frac{n_J}{Y_J}) \sum_{i:X_i = t_J} M_i(t_J) - \frac{n_J}{Y_J} \sum_{i:X_i \geq t_J} M_i(t_J) \\
= & (1 + \frac{n_J}{Y_J}) \{ \sum_{i:X_i = t_J} M_i(t_J) - \frac{n_J}{Y_J + n_J} \sum_{i:X_i \geq t_J} M_i(t_J) \} \\
= & (1 + \frac{n_J}{Y_J}) M^*(t_J). \qquad (18)
\end{aligned}$$

Now we move to the 2nd largest censoring time t_{J-1}, where the number of subjects surviving longer than t_{J-1} is Y_{J-1}. The RRimp cost for the kth censored subject at

t_{J-1} is

$$
\begin{aligned}
& M_{J-1,k}^{RRimp} \\
= \ & M_k(t_{J-1}) + \frac{1}{Y_{J-1}} \sum_{i:X_i>t_{J-1}} \{M_i - M_i(t_{J-1})\} \\
= \ & M_k(t_{J-1}) + \frac{1}{Y_{J-1}} \{ \sum_{i:X_i>t_{J-1}} \Delta_i [M_i - M_i(t_{J-1})] \\
& + \sum_{i:X_i=t_J} [M_{J,i}^{RRimp} - M_i(t_{J-1})] \} \\
= \ & M_k(t_{J-1}) + \frac{1}{Y_{J-1}} \{ \sum_{i:X_i>t_{J-1}} \Delta_i M_i - \sum_{i:X_i>t_{J-1}} \Delta_i M_i(t_{J-1}) \\
& - \sum_{i:X_i=t_J} M_i(t_{J-1}) + \sum_{i:X_i=t_J} M_i(t_J) + \frac{n_J}{Y_J} \sum_{i:X_i>t_J} \Delta_i [M_i - M_i(t_J)] \} \\
= \ & M_k(t_{J-1}) + \frac{1}{Y_{J-1}} \{ \sum_{i:X_i>t_J} \Delta_i M_i + \sum_{i:t_{J-1}<X_i\le t_J} \Delta_i M_i - \sum_{i:X_i>t_{J-1}} M_i(t_{J-1}) \\
& + \sum_{i:X_i=t_J} M_i(t_J) + \frac{n_J}{Y_J} \sum_{i:X_i>t_J} \Delta_i M_i - \frac{n_J}{Y_J} \sum_{i:X_i>t_J} M_i(t_J) \} \\
= \ & \frac{1}{Y_{J-1}} (1 + \frac{n_J}{Y_J}) \sum_{i:X_i>t_J} \Delta_i M_i + \frac{1}{Y_{J-1}} \sum_{i:t_{J-1}<X_i\le t_J} \Delta_i M_i + M_k(t_{J-1}) \\
& - \frac{1}{Y_{J-1}} \sum_{i:X_i>t_{J-1}} M_i(t_{J-1}) + \frac{1}{Y_{J-1}} \sum_{i:X_i=t_J} M_i(t_J) - \frac{n_J}{Y_J Y_{J-1}} \sum_{i:X_i>t_J} M_i(t_J)
\end{aligned}
$$

where the first two terms $\frac{1}{Y_{J-1}}(1 + \frac{n_J}{Y_J}) \sum_{i:X_i>t_J} \Delta_i M_i + \frac{1}{Y_{J-1}} \sum_{i:t_{J-1}<X_i\le t_J} \Delta_i M_i = M_{J-1}^{RR}$ (Zhao et al. 2011). Thus, the sum of difference between $M_{J-1,k}^{RRimp}$ and M_{J-1}^{RR} at

t_{J-1} is

$$\begin{aligned}
&\sum_{k:X_k=t_{J-1}} (M^{RRimp}_{J-1,k} - M^{RR}_{J-1}) \\
= &\sum_{i:X_i=t_{J-1}} M_i(t_{J-1}) - \frac{n_{J-1}}{Y_{J-1}} \sum_{i:X_i>t_{J-1}} M_i(t_{J-1}) + \frac{n_{J-1}}{Y_{J-1}} \sum_{i:X_i=t_J} M_i(t_J) \\
&- \frac{n_{J-1}n_J}{Y_{J-1}Y_J} \sum_{i:X_i>t_J} M_i(t_J) \\
= &(1+\frac{n_{J-1}}{Y_{J-1}}) \sum_{i:X_i=t_{J-1}} M_i(t_{J-1}) - \frac{n_{J-1}}{Y_{J-1}} \sum_{i:X_i\geq t_{J-1}} M_i(t_{J-1}) \\
&+ \frac{n_{J-1}}{Y_{J-1}}(1+\frac{n_J}{Y_J}) \sum_{i:X_i=t_J} M_i(t_J) - \frac{n_{J-1}n_J}{Y_{J-1}Y_J} \sum_{i:X_i\geq t_J} M_i(t_J) \\
= &(1+\frac{n_{J-1}}{Y_{J-1}})M^*(t_{J-1}) + \frac{n_{J-1}}{Y_{J-1}}(1+\frac{n_J}{Y_J})M^*(t_J) \qquad (19)
\end{aligned}$$

Similarly, we have

$$\begin{aligned}
&\sum_{k:X_k=t_{J-2}} (M^{RRimp}_{J-2,k} - M^{RR}_{J-2}) \\
= &(1+\frac{n_{J-2}}{Y_{J-2}})M^*(t_{J-2}) + \frac{n_{J-2}}{Y_{J-2}}(1+\frac{n_{J-1}}{Y_{J-1}})M^*(t_{J-1}) \\
&+ \frac{n_{J-2}}{Y_{J-2}}(1+\frac{n_{J-1}}{Y_{J-1}})(1+\frac{n_J}{Y_J})M^*(t_J) \qquad (20)
\end{aligned}$$

In (18), the contribution of $M^*(t_j)$ is $(1+\frac{n_J}{Y_J})$. In (19), its contribution is $\frac{n_{J-1}}{Y_{J-1}}(1+\frac{n_J}{Y_J})$. For (20), the contribution is $\frac{n_{J-2}}{Y_{J-2}}(1+\frac{n_{J-1}}{Y_{J-1}})(1+\frac{n_J}{Y_J})$. If we generalize the conclusion and sum up the equations from J to 1, we can find the contribution of $M^*(t_J)$ is

$$\begin{aligned}
&\left(1+\frac{n_J}{Y_J}\right) + \left(1+\frac{n_J}{Y_J}\right)\cdot\frac{n_{J-1}}{Y_{J-1}} + \cdots + \left(1+\frac{n_J}{Y_J}\right)\cdots\left(1+\frac{n_2}{Y_2}\right)\cdot\frac{n_1}{Y_1} \\
= &\prod_{j=1}^{J}\left(1+\frac{n_j}{Y_j}\right).
\end{aligned}$$

Similarly, the contribution of $M^*(t_j)$ is

$$\left(1+\frac{n_j}{Y_j}\right)+\left(1+\frac{n_j}{Y_j}\right)\cdot\frac{n_{j-1}}{Y_{j-1}}+\cdots+\left(1+\frac{n_j}{Y_j}\right)\cdots\left(1+\frac{n_2}{Y_2}\right)\cdot\frac{n_1}{Y_1}=\prod_{l=1}^{j}\left(1+\frac{n_l}{Y_l}\right).$$

Hence,

$$\begin{aligned}
&\hat{\mu}_{RRimp} \\
= &\ \frac{1}{n}\{\sum_{i=1}^{n}\Delta_i M_i+\sum_{k:X_k=t_J}M_{J,k}^{RRimp}+\sum_{k:X_k=t_{J-1}}M_{J-1,k}^{RRimp}+\cdots+\sum_{k:X_k=t_1}M_{1,k}^{RRimp}\} \\
= &\ \frac{1}{n}\{\sum_{i=1}^{n}\Delta_i M_i+\sum_{k:X_k=t_J}M_J^{RR}+\sum_{k:X_k=t_{J-1}}M_{J-1}^{RR}+\cdots+\sum_{k:X_k=t_1}M_1^{RR}\} \\
&+\frac{1}{n}\{\prod_{j=1}^{J}(1+\frac{n_j}{Y_j})M^*(t_J)+\prod_{j=1}^{J-1}(1+\frac{n_j}{Y_j})M^*(t_{J-1})+\cdots+(1+\frac{n_1}{Y_1})M^*(t_1)\} \\
= &\ \hat{\mu}_{RR}+\frac{1}{n}\{\prod_{j=1}^{J}(1+\frac{n_j}{Y_j})M^*(t_J)+\prod_{j=1}^{J-1}(1+\frac{n_j}{Y_j})M^*(t_{J-1})+\cdots+(1+\frac{n_1}{Y_1})M^*(t_1)\}
\end{aligned}$$

Where $\hat{\mu}_{RR}=\hat{\mu}_{BT}$ is already known, and $M^*(t_j)=\sum_{i:X_i=t_j}[M_i(t_j)-\overline{M(t_j)}]$ according to its definition. It can also be shown that the Kaplan-Meier estimator for $K(t_j)$ is

$$\hat{K}(t_j)=\prod_{l=1}^{j}\frac{Y_l}{Y_l+n_l},$$

which means

$$\frac{1}{\hat{K}(t_j)}=\frac{1}{\prod_{l=1}^{j}\frac{Y_l}{Y_l+n_l}}=\prod_{l=1}^{j}\left(1+\frac{n_l}{Y_l}\right).$$

Thus,

$$
\begin{aligned}
& \hat{\mu}_{RRimp} \\
= \; & \hat{\mu}_{BT} + \frac{1}{n}\{\frac{\sum_{i:X_i=t_J}[M_i(t_J) - \overline{M(t_J)}]}{\hat{K}(t_J)} + \frac{\sum_{i:X_i=t_{J-1}}[M_i(t_{J-1}) - \overline{M(t_{J-1})}]}{\hat{K}(t_{J-1})} \\
& + \frac{\sum_{i:X_i=t_{J-2}}[M_i(t_{J-2}) - \overline{M(t_{J-2})}]}{\hat{K}(t_{J-2})} + \cdots + \frac{\sum_{i:X_i=t_1}[M_i(t_1) - \overline{M(t_1)}]}{\hat{K}(t_1)}\} \\
= \; & \hat{\mu}_{BT} + \frac{1}{n}\sum_{i=1}^{n}\frac{(1-\Delta_i)[M_i - \overline{M(C_i)}]}{\hat{K}(C_i)} \\
= \; & \hat{\mu}_{ZT}.
\end{aligned}
$$

We have proved that the RRimp estimator is the same as the ZT estimator for estimating the mean cost.

APPENDIX C

PROOF OF ASYMPTOTIC UNBIASEDNESS OF THE RRIMP^K ESTIMATOR

Since we focus on time-restricted costs, and set $T_i = L$ or $C_i = L$ if the time exceeds L, we can assume $T_i \leq L$ and $C_i \leq L$.

It is easy to see

$$\begin{aligned} &E\{\hat{S}_{RRimpK,n,h_n}(x)\} = Pr(M_i > x, \Delta_i = 1) + Pr(\Delta_i = 0) \cdot \\ &E[\frac{E\{\frac{\Delta_j I(T_j > C_i)}{h_n S^T(C_i) K(T_j)} w(\frac{u}{h_n}) I(M_j + u > x) | C_i, M_i(C_i)\}}{E\{\frac{\Delta_j I(T_j > C_i)}{h_n S^T(C_i) K(T_j)} w(\frac{u}{h_n}) | C_i, M_i(C_i)\}} + O_p(\frac{1}{n}) | T_i > C_i]. \quad (21) \end{aligned}$$

For the denominator in (21), let $u = h_n \tilde{u}$, with Bounded convergence theorem,

$$\begin{aligned} & \lim_{h_n \to 0} E\{\frac{\Delta_j I(T_j > C_i)}{h_n S^T(C_i) K(T_j)} w(\frac{u}{h_n}) | C_i, M_i(C_i)\} \\ = \ & \frac{\int_{T_j}^{L} \mathrm{d}P(C_j)}{K(T_j)} \int_{-\infty}^{\infty} \int_{C_i}^{L} \int_{M_i(C_i)}^{\infty} \lim_{h_n \to 0} \frac{w(\tilde{u})}{S^T(C_i)} f\{T_j, M_j, h_n \tilde{u} | C_i, M_i(C_i)\} \mathrm{d}M_j \mathrm{d}T_j \mathrm{d}\tilde{u} \\ = \ & \int_{-\infty}^{\infty} \int_{C_i}^{L} \int_{M_i(C_i)}^{\infty} \frac{w(\tilde{u})}{S^T(C_i)} f\{T_j, M_j | M_j(C_i) = M_i(C_i)\} \mathrm{d}M_j \mathrm{d}T_j \mathrm{d}\tilde{u} \\ = \ & \frac{\int_{-\infty}^{\infty} w(\tilde{u}) \mathrm{d}\tilde{u}}{S^T(C_i)} \int_{C_i}^{L} \int_{M_i(C_i)}^{\infty} f\{T_j, M_j | M_j(C_i) = M_i(C_i)\} \mathrm{d}M_j \mathrm{d}T_j \\ = \ & \int_{-\infty}^{\infty} w(\tilde{u}) \mathrm{d}\tilde{u}. \end{aligned}$$

For the numerator in (21), given $\epsilon > 0$, divide $[M_i(C_i), \infty)$ to be $D_1 = [M_i(C_i), x - \epsilon] \cup [x + \epsilon, \infty)$ and $D_2 = (x - \epsilon, x + \epsilon)$. Since $I(M_j + h_n \tilde{u} > x)$ does not change for small h_n given fixed $\tilde{u}$ and $M_j \in D_1$, we have

$$\begin{aligned}
& \lim_{h_n \to 0} E\{\frac{\Delta_j I(T_j > C_i)}{n h_n S^T(C_i) K(T_j)} w(\frac{u}{h_n}) I(M_j + u > x) | C_i, M_i(C_i)\} \\
= & \int_{-\infty}^{\infty} \int_{C_i}^{L} \int_{D_1} \lim_{h_n \to 0} \frac{w(\tilde{u}) I(M_j + h_n \tilde{u} > x)}{S^T(C_i)} f\{T_j, M_j, h_n \tilde{u} | C_i, M_i(C_i)\} \mathrm{d}M_j \mathrm{d}T_j \mathrm{d}\tilde{u} \\
& + \lim_{h_n \to 0} \int_{-\infty}^{\infty} \int_{C_i}^{L} \int_{D_2} \frac{w(\tilde{u}) I(M_j + h_n \tilde{u} > x)}{S^T(C_i)} f\{T_j, M_j, h_n \tilde{u} | C_i, M_i(C_i)\} \mathrm{d}M_j \mathrm{d}T_j \mathrm{d}\tilde{u} \\
= & \int_{-\infty}^{\infty} \int_{C_i}^{L} \int_{D_1} \frac{w(\tilde{u}) I(M_j > x)}{S^T(C_i)} f\{T_j, M_j, 0 | C_i, M_i(C_i)\} \mathrm{d}M_j \mathrm{d}T_j \mathrm{d}\tilde{u} \\
& + \lim_{h_n \to 0} \int_{-\infty}^{\infty} \int_{C_i}^{L} \int_{D_2} \frac{w(\tilde{u}) I(M_j + h_n \tilde{u} > x)}{S^T(C_i)} f\{T_j, M_j, h_n \tilde{u} | C_i, M_i(C_i)\} \mathrm{d}M_j \mathrm{d}T_j \mathrm{d}\tilde{u} \\
= & \int_{-\infty}^{\infty} \int_{C_i}^{L} \int_{D_1} \frac{w(\tilde{u}) I(M_j > x)}{S^T(C_i)} f\{T_j, M_j, 0 | C_i, M_i(C_i)\} \mathrm{d}M_j \mathrm{d}T_j \mathrm{d}\tilde{u} + R
\end{aligned}$$

Let $\epsilon \to 0$, the first term becomes

$$\begin{aligned}
& \lim_{\epsilon \to 0} \frac{\int_{-\infty}^{\infty} w(\tilde{u}) \mathrm{d}\tilde{u}}{S^T(C_i)} \int_{C_i}^{L} \int_{D_1} I(M_j > x) f\{T_j, M_j, 0 | C_i, M_i(C_i)\} \mathrm{d}M_j \mathrm{d}T_j \\
= & \; Pr\{M_j > x, M_j(C_i) = M_i(C_i) | C_i, M_i(C_i)\} \cdot \int_{-\infty}^{\infty} w(\tilde{u}) \mathrm{d}\tilde{u}.
\end{aligned}$$

With $\epsilon \to 0$, the second term R becomes

$$\begin{aligned}
& \lim_{\epsilon \to 0} R \\
\leq & \lim_{\epsilon \to 0} \lim_{h_n \to 0} \int_{-\infty}^{\infty} \int_{C_i}^{L} \int_{D_2} \frac{w(\tilde{u})}{S^T(C_i)} f\{T_j, M_j, h_n \tilde{u} | C_i, M_i(C_i)\} \mathrm{d}M_j \mathrm{d}T_j \mathrm{d}\tilde{u} \\
\leq & \lim_{\epsilon \to 0} \lim_{h_n \to 0} \int_{-\infty}^{\infty} \int_{C_i}^{L} \int_{D_2} \frac{w(\tilde{u}) B}{S^T(C_i)} \mathrm{d}M_j \mathrm{d}T_j \mathrm{d}\tilde{u} \\
= & \lim_{\epsilon \to 0} 2\epsilon (L - C_i) \frac{B}{S^T(C_i)} \int_{-\infty}^{\infty} w(\tilde{u}) \mathrm{d}\tilde{u} \\
= & \; 0,
\end{aligned}$$

where f is bounded with $|f| \leq B$.

Thus,

$$
\begin{aligned}
& \lim_{h_n \to 0} E\{\frac{\Delta_j I(T_j > C_i)}{nh_n S^T(C_i)K(T_j)} w(\frac{u}{h_n}) I(M_j + u > x) | C_i, M_i(C_i)\} \\
= \quad & Pr\{M_j > x, M_j(C_i) = M_i(C_i) | C_i, M_i(C_i)\} \cdot \int_{-\infty}^{\infty} w(\tilde{u}) \mathrm{d}\tilde{u}.
\end{aligned}
$$

Therefore,

$$
\begin{aligned}
& \lim_{n \to \infty} E[\frac{E\{\frac{\Delta_j I(T_j > C_i)}{h_n S^T(C_i)K(T_j)} w(\frac{u}{h_n}) I(M_j + u > x) | C_i, M_i(C_i)\}}{E\{\frac{\Delta_j I(T_j > C_i)}{h_n S^T(C_i)K(T_j)} w(\frac{u}{h_n}) | C_i, M_i(C_i)\}} + O_p(\frac{1}{n}) | T_i > C_i] \\
& \cdot Pr(\Delta_i = 0) \\
= \quad & \lim_{h_n \to 0} \int_D \frac{E\{\frac{\Delta_j I(T_j > C_i)}{nh_n S^T(C_i)K(T_j)} w(\frac{u}{h_n}) I(M_j + u > x) | C_i, M_i(C_i)\}}{E\{\frac{\Delta_j I(T_j > C_i)}{nh_n S^T(C_i)K(T_j)} w(\frac{u}{h_n}) | C_i, M_i(C_i)\}} dP\{C_i, T_i, M_i(C_i) \\
= \quad & \int_D Pr\{M_j > x, M_j(C_i) = M_i(C_i) | C_i, M_i(C_i)\} dP\{C_i, T_i, M_i(C_i)\} \\
= \quad & \int_D Pr(M_i > x) dP\{C_i, T_i, M_i(C_i)\} \\
= \quad & Pr(M_i > x, T_i > C_i)
\end{aligned}
$$

where $D = \{C_i, T_i, M_i(C_i) : L \geq T_i > C_i \geq 0, M_i(C_i) \geq 0\}$, and the last second equality is from Marcov property of cost process.

Combining the above results with (21), we have proved the theorem.